S. Hossein Fatemi
Paula J. Clayton
Editors

The Medical Basis of Psychiatry

Fourth Edition

Springer

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Fourth Edition

Edited by

S. Hossein Fatemi, M.D., Ph.D.
University of Minnesota, Minneapolis, MN, USA

Paula J. Clayton, M.D.
Formerly of, University of Minnesota, Minneapolis, MN, USA

Springer

Editors
S. Hossein Fatemi, M.D., Ph.D., FACPsych
Professor of Psychiatry and Neuroscience
University of Minnesota School of Medicine
420 Delaware St SE, MMC 392
Minneapolis, MN 55455, USA

Paula J. Clayton, M.D.
Professor Emerita,
University of Minnesota School of Medicine,
University of New Mexico School of Medicine
Pasadena, CA 91103, USA

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To George Winokur

S.H.F. and P.J.C.

To my father, S. Mehdi Fatemi, and to my family, S. Ali Fatemi, M.D., Naheed Fatemi, Parvin Fatemi, S. Mohammad Fatemi, Neelufaar Fatemi, Maryam Jalali-Mousavi, Ph.D., and last but not least, my mother, Fatemeh Parsa Moghaddam, whose love and support have enabled me to complete this work, and to my first teacher in psychiatry, Deborah Gould, M.D.

S.H.F.

To my children, who have tolerated my passion for work and psychiatry: Clarissa Beth Weirick, Matthew Charles Clayton, and Andrew Curtis Clayton, to George and his lovely family and to all those at Washington University Department of Psychiatry who taught me and inspired me.

P.J.C.

Foreword

This fourth edition of a classic American textbook of neuromedically oriented psychiatry continues an important tradition reflected in the first edition of 1986 (599 pp) from WB Saunders Press, edited by the late George Winokur, MD, with Professor Clayton, continued with the second edition of 1994 (603 pp), and the third and fourth editions with Professor S. Hossein Fatemi as co-editor in 2008 (799 pp) from Humana Press, a division of Springer. The orientation of the book grew out of a descriptive neuromedical approach to psychiatry that was characteristic of 19th and early 20th century European psychiatry, and largely lost in psychodynamically dominated mid-20th-century American psychiatry. More specifically, it reflects the interests of a most notable and unusual department of psychiatry at Washington University in St. Louis led by Professor Eli Robins and his colleagues, where Dr. Clayton trained, and where Dr. Winokur worked for many years before becoming chairman of psychiatry at the University of Iowa. The present edition is based at the University of Minnesota and is again edited by Drs. Fatemi and Clayton. Most of the 81 authors of this edition are from Midwestern American institutions.

This fourth edition has 1064 pages, with 43 chapters organized into four parts: I. Adult Syndromes (17 chapters), II. Child Psychiatry (5 chapters), III. Symptom Clusters (6 chapters), and IV. Special Areas (15 chapters). Diagnosis largely follows DSM-5 criteria. For a complex, multiauthored product, there is substantial uniformity of organization and referencing, which is extensive. Topics addressed in considerable detail include those expected of a medically oriented text, such as neuroimaging, genetics, and psychopharmacology, as well as consideration of therapeutic brain stimulation and psychosurgery. An interesting discussion addresses findings from basic neuroscience from the perspective of potential therapeutic innovations, and there are useful summaries of psychometric rating scales and of normal laboratory testing values and typical serum concentrations of psychotropic drugs. Forensic psychiatry is covered, and there is a single chapter on psychological treatments, based heavily on behavioral and cognitive methods. A particularly clinically and educationally useful section considers symptom clusters or syndromes rather than "disorders" in the somewhat narrower DSM tradition. A unique chapter presents brief biographical sketches of noteworthy historical figures in psychiatry and neuroscience—ranging from ancients, through 19th and 20th century leaders, to living neuroscientists and pharmacologists.

Overall, this somewhat enlarged volume very effectively continues the valuable tradition started by Drs. Winokur and Clayton in 1986, and ably continued by Drs. Fatemi and Clayton. The fourth edition continues as a leading and novel textbook of psychiatry with a strong neuromedical orientation. It can be highly recommended for students, trainees, and professionals working in this complex and constantly evolving field.

Ross J. Baldessarini, MD
Professor of Psychiatry
Harvard Medical School
Boston, Massachusetts

Preface

It has been 8 years since the last edition of *The Medical Basis of Psychiatry* was published. The third edition of the book was quite successful in terms of readership and received overwhelmingly positive reviews from the scientific community. As numerous changes have occurred in the field of psychiatry including advances in neuroscience of the brain, genetics, pharmacology, and etiology of brain disorders, it was deemed necessary to update the book again to collect all of the newest information for clinicians and students. All chapters have been updated and some new topics have also been added such as a discussion of neuromodulation and rating scales in psychiatry. Additionally, details about several new medications introduced since 2008 have been added to the book. We are grateful to all of the chapter authors who have updated the book. We are hopeful that this edition meets with the approval of the readership.

Minneapolis, MN, USA
Pasadena, CA, USA

S. Hossein Fatemi, M.D., Ph.D.
Paula J. Clayton, M.D.

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Contributors

Hagop S. Akiskal, M.D. Professor and Director of International Mood Center, Department of Psychiatry, and Division of International Health and Cross-Cultural Medicine, University of California at San Diego, La Jolla, CA, USA

Nancy C. Andreasen, M.D., Ph.D. The Andrew H. Woods Chair of Psychiatry, Director, Mental Health Clinical Research Center, Department of Psychiatry, University of Iowa Carver College of Medicine, Iowa City, IA, USA

Afshan Anjum, M.D. Assistant Professor, Department of Psychiatry, University of Minnesota School of Medicine, Minneapolis, MN, USA

Gail A. Bernstein, M.D. Endowed Professor in Child and Adolescent Anxiety Disorders, Head, Program in Child and Adolescent Anxiety and Mood Disorders, Division of Child and Adolescent Psychiatry, University of Minnesota Medical School, Minneapolis, MN, USA

Wade Berrettini, M.D., Ph.D. Professor, Department of Psychiatry, University of Pennsylvania, Director, Center for Neurobiology and Behavior, Philadelphia, PA, USA

Dan G. Blazer, M.D. Ph.D J.P. Gibbons Professor of Psychiatry, Department of Psychiatry and Behavioral Sciences, Duke University Medical Center, Durham, NC, USA

Ana Bortnova, B.A. Research Assistant, Department of Psychiatry, University of Minnesota School of Medicine, Minneapolis, MN, USA

Victoria Brown-Nyseth, M.D. Department of Psychiatry, Minneapolis Veterans Affairs Medical Center, University of Minnesota School of Medicine, Minneapolis, MN, USA

Paula J. Clayton, M.D. Professor Emerita, University of Minnesota School of Medicine and University of New Mexico School of Medicine, Pasadena, CA, USA

C. Robert Cloninger, M.D. Wallace Renard Professor of Psychiatry, Department of Psychiatry, Washington University School of Medicine, St. Louis, MO, USA

William Coryell, M.D. George Winokur Professor of Psychiatry, Department of Psychiatry, University of Iowa Carver College of Medicine, Iowa City, IA, USA

Scott J. Crow, M.D. Professor, Department of Psychiatry, University of Minnesota School of Medicine, Minneapolis, MN, USA

Kathryn R. Cullen, M.D. Assistant Professor, Department of Psychiatry, University of Minnesota School of Medicine, Minneapolis, MN, USA

Dianne Currier, Ph.D. Senior Research Fellow, Centre for Molecular, Environmental, Genetic and Analytic Epidemiology, Melbourne School of Population Health, The University of Melbourne, Carlton, Victoria, Australia

Susan Czapiewski, M.D., M.S. Assistant Professor, Department of Psychiatry, University of Minnesota School of Medicine, Minneapolis Veterans Affairs Medical Center, Minneapolis, MN, USA

Inna D'Empaire, M.D. Associate Professor, Director of Consultation-Liaison Service, Department of Psychiatry and Behavioral Sciences, University of Kansas School of Medicine-Wichita, and Clinical Research Institute, Wichita, KS, USA

Milind Deogaonkar, M.D., M.Ch. Associate Professor, Department of Neurosurgery, Center of Neuromodulation, Wexner Medical Center, The Ohio State University, Columbus, OH, USA

Karen J. Derefinko, Ph.D. Postdoctoral Fellow, Department of Psychology, University of Kentucky, Lexington, KY, USA

Dirk M. Dhossche, M.D., Ph.D. Professor, Department of Psychiatry, University of Mississippi Medical Center, Jackson, MS, USA

Mehmet Dokucu, M.D., Ph.D. Assistant Professor, Department of Psychiatry and Behavioral Sciences, Northwestern University Feinberg School of Medicine, Chicago, IL, USA

Elke D. Eckert, M.D. Professor, Department of Psychiatry, University of Minnesota School of Medicine, Minneapolis, MN, USA

Neelufaar Fatemi, B.S. University of Minnesota, Minneapolis, MN, USA

S. Ali Fatemi, M.D. Attending Cardiologist, Farabi Hospital, Tehran, Iran

S. Hossein Fatemi, M.D., Ph.D., FACPsych Associate Chair for Neuroscience and Translational Research, Bernstein Endowed Chair in Adult Psychiatry, Professor, Departments of Psychiatry and Neuroscience, University of Minnesota School of Medicine, Minneapolis, MN, USA

Timothy D. Folsom, M.S. Junior Scientist, Department of Psychiatry, University of Minnesota School of Medicine, Minneapolis, MN, USA

Edward S. Friedman, M.D. Associate Professor, Department of Psychiatry, University of Pittsburgh Medical Center, Western Psychiatric Institute Clinic, Pittsburgh, PA, USA

Matthew A. Fuller, Pharm.D., BCPS, BCPP, FASHP Clinical Pharmacy Specialist, Department of Psychiatry, Louis Stokes Cleveland Department of Veterans Affairs Medical Center; Associate Clinical Professor, Department of Psychiatry, Clinical Instructor, Department of Psychology, Case Western Reserve University, Cleveland, OH, USA; Adjunct Associate Professor of Clinical Pharmacy, University of Toledo, Toledo, OH, USA

Aintzane García-Bea, B.Pharm. Graduate Student, Department of Pharmacology, Faculty of Medicine and Odontology, University of the Basque Country, Bizkaia, Spain

Danielle Goerke, D.O. Assistant Professor, Department of Psychiatry, University of Minnesota School of Medicine, Minneapolis, MN, USA

Michal Goetz, M.D., Ph.D. Assistant Professor, Department of Child Psychiatry, University Hospital Motol, Charles University, Prague, Czech Republic

Javier González-Maeso, Ph.D. Assistant Professor, Departments of Psychiatry and Neurology, Friedman Brain Institute, Leon and Norma Hess Center for Science and Medicine, Icahn School of Medicine at Mount Sinai, New York, NY, USA

Jon E. Grant, M.D., J.D. Professor, Department of Psychiatry and Behavioral Neuroscience, University of Chicago Pritzker School of Medicine, Chicago, IL, USA

Thomas D. Hurwitz, M.D. Assistant Professor, Department of Psychiatry, University of Minnesota School of Medicine; Department of Psychiatry, Minneapolis VA Medical Center; Minnesota Regional Sleep Disorders Center, Hennepin County Medical Center, Minneapolis, MN, USA

Celia F. Hybels, Ph.D. Associate Professor, Department of Psychiatry and Behavioral Sciences, Duke University Medical Center, Durham, NC, USA

Alexandra Junewicz, M.D. Resident, Department of Psychiatry, New York University School of Medicine, New York City, NY, USA

Imran S. Khawaja, MBBS, FAASM Minnesota Regional Sleep Disorders Center, Hennepin County Medical Center; Department of Neurology, University of Minnesota, Minneapolis, MN, USA

Suck Won Kim, M.D. Professor, Department of Psychiatry, University of Minnesota Medical School, Minneapolis, MN, USA

Aaron M. Koenig, M.D. Resident, Department of Psychiatry, University of Pittsburgh Medical Center, Pittsburgh, PA, USA

Mitsumasa Kurita, Ph.D. Senior Research Scientist, Dainippon Sumitomo Pharma Co., Ltd., Osaka, Japan

Matthew Macaluso, D.O. Assistant Professor, Department of Psychiatry and Behavioral Sciences, University of Kansas School of Medicine-Wichita, Wichita, KS, USA

J. John Mann, M.D. Paul Janssen Professor of Translational Neuroscience, Department of Psychiatry, Columbia University, Chief, Department of Neuroscience, New York State Psychiatric Institute, New York, NY, USA

Amelia Merz, M.D. Psychiatrist, Edward Hines Jr. Veterans Affairs Hospital, Hines, IL, USA

Elena B. Metcalf, M.D. Fellow, Department of Psychiatry, Division of Child and Adolescent Psychiatry, University of Minnesota School of Medicine, Minneapolis, MN, USA

Tanya K. Murphy, M.D. Maurice A. and Thelma P. Rothman Chair of Developmental Pediatrics, Director, Rothman Center for Pediatric Neuropsychiatry, Professor, Departments of Pediatrics and Psychiatry and Behavioral Neurosciences, Rothman Center for Neuropsychiatry, Department of Psychiatry, University of South Florida, St. Petersburg, FL, USA

Alexander B. Niculescu III, M.D., Ph.D. Associate Professor, Department of Psychiatry, Institute of Psychiatric Research, Indiana University School of Medicine, Indianapolis, IN, USA

John I. Nurnberger Jr., M.D., Ph.D. Joyce and Iver Small Professor, Department of Psychiatry, Director, Institute of Psychiatric Research, Indiana University School of Medicine, Indianapolis, IN, USA

Demian Obregon, M.D. Department of Psychiatry and Behavioral Neurosciences, University of South Florida, USF Health, Morsani College of Medicine, St. Petersburg, FL, USA

Cheryl A. Olman, Ph.D. Associate Professor, Departments of Psychology and Radiology, Center for Magnetic Resonance Research, University of Minnesota, Minneapolis, MN, USA

Lewis Opler, M.D., Ph.D. Clinical Professor, Department of Psychiatry, Columbia University College of Physicians and Surgeons, New York City, NY, USA

Mark Opler, Ph.D., M.P.H. Assistant Professor, Departments of Psychiatry and Environmental Medicine, New York University School of Medicine, New York City, NY, USA

José V. Pardo, Ph.D., M.D. Professor, Department of Psychiatry, University of Minnesota School of Medicine; Director, Cognitive Neuroimaging Unit, VA Medical Center, Minneapolis, MN, USA

Patricia J. Pardo, Ph.D. Assistant Professor, Departments of Psychiatry and Psychology, University of Minnesota, Brain Sciences Center, Minneapolis Veterans Affairs Medical Center, Minneapolis, MN, USA

Sheldon H. Preskorn, M.D. Professor, Department of Psychiatry and Behavioral Sciences, University of Kansas School of Medicine-Wichita, Wichita, KS, USA

Taylor C. Preston, M.D. Assistant Professor, Department of Psychiatry and Behavioral Neurobiology, The University of Alabama at Birmingham, Birmingham, AL, USA

Nancy C. Raymond, M.D. Professor, Department of Psychiatry, University of Minnesota School of Medicine, Minneapolis, MN, USA

George M. Realmuto, M.D. Professor, Department of Psychiatry, University of Minnesota School of Medicine, Minneapolis, MN, USA

Phillip J. Resnick, M.D. Professor, Department of Psychiatry, Director, Division of Forensic Psychiatry, Case Western Reserve University School of Medicine, Cleveland, OH, USA

Ali Rezai, M.D. Professor and Stanley D. and Joan H. Ross Chair in Neuromodulation, Director, Neuroscience Program and Center for Neuromodulation, Wexner Medical Center, The Ohio State University, Columbus, OH, USA

Barry R. Rittberg, M.D. Assistant Professor, Department of Psychiatry, University of Minnesota School of Medicine, Minneapolis, MN, USA

Marc-Andre Roy, M.D., FRCPC Professeur Agrégé, Département de Psychiatrie et Neurosciences, Université Laval, Centre de Recherche de l'Institut Universitaire en Santé Mentale de Québec City, Québec, Canada

Martha Sajatovic, M.D. Professor, Departments of Psychiatry and Neurology, Case Western Reserve University, Director, Neurological and Behavioral Outcomes Center, University Hospitals of Cleveland, Cleveland, OH, USA

Carlos H. Schenck, M.D. Professor, Department of Psychiatry, University of Minnesota School of Medicine; Department of Psychiatry, Minnesota Regional Sleep Disorders Center, Hennepin County Medical Center, Minneapolis, MN, USA

S. Charles Schulz, M.D. Professor, Donald W. Hastings Endowed Chair, Department of Psychiatry, University of Minnesota School of Medicine, Minneapolis, MN, USA

Charles L. Scott, M.D. Associate Clinical Professor of Psychiatry, Chief, Division of Psychiatry and the Law, Department of Psychiatry and Behavioral Sciences, University of California at Davis, Davis, CA, USA

Mayur Sharma, M.D., M.Ch. Fellow, Center of Neuromodulation, Wexner Medical Center, The Ohio State University, Columbus, OH, USA

William Sheehan, M.D. Psychiatrist, Child and Adolescent Behavior Health Services, Willmar, MN, USA

Richard C. Shelton, M.D. Charles Byron Ireland Professor, Department of Psychiatry and Behavioral Neurobiology, The University of Alabama at Birmingham, Birmingham, AL, USA

Pascal Sienaert, M.D., Ph.D. Assistant Professor, Department of Psychiatry, University Psychiatric Center – Catholic University of Leuven, campus Kortenberg, Kortenberg, Belgium

S. Evelyn Stewart, M.D. Director, Pediatric OCD Program, Associate Professor of Psychiatry, University of British Columbia; Senior Clinician Scientist, Child and Family Research Institute, Vancouver, British Columbia, Canada

Dragan M. Svrakic, M.D., Ph.D. Professor, Department of Psychiatry, Washington University School of Medicine, St. Louis, MO, USA

Michael E. Thase, M.D. Professor, Department of Psychiatry, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, USA

Steven Thurber, Ph.D., ABPP Child and Adolescent Behavior Health Services, Minnesota Department of Human Services, Willmar, MN, USA

Charles Van Valkenburg, M.D. Alabama Clinics, Dothan, AL, USA

Andrea M. Victor, Ph.D. Psychologist, Chicago Neurodevelopmental Center, Chicago, IL, USA

Lee Elizabeth Wachtel, M.D. Associate Professor, Department of Psychiatry, Johns Hopkins University, School of Medicine; Medical Director, Neurobehavioral Unit, Kennedy Krieger Institute, Baltimore, MD, USA

Joseph Westermeyer, M.D., M.P.H., Ph.D. Professor, Department of Psychiatry, University of Minnesota School of Medicine, Staff Psychiatrist, Addictive Disorders Service, Mental Health Service, Minneapolis VA Medical Center, Minneapolis, MN, USA

Thomas A. Widiger, Ph.D. Professor, Department of Psychology, University of Kentucky, Lexington, KY, USA

William R. Yates, M.D. Professor of Research, Department of Psychiatry, University of Oklahoma College of Medicine, Tulsa, OK, USA

Gihyun Yoon, M.D. Assistant Professor of Psychiatry, University of Minnesota, Staff Psychiatrist, Addictive Disorder Team, Mental Health Service, Minneapolis VA Medical Center, Minneapolis, MN, USA

Alexandra D. Zagoloff, Ph.D. Assistant Professor, Department of Psychiatry, Division of Child and Adolescent Psychiatry, University of Minnesota School of Medicine, Minneapolis, MN, USA

Zion Zibly, M.D. Fellow, Center of Neuromodulation, Wexner Medical Center, The Ohio State University, Columbus, OH, USA

Part I
Syndromes: Adult

1
The Mental Status Examination

Hagop S. Akiskal, M.D.

Abstract The Mental Status Examination represents a crucial part of the psychiatric interview in that it is devoted to a systematic elicitation of psychopathologic signs and symptoms that are important in diagnosis and differential diagnosis. It is an essential tool for all psychiatrists and mental health professionals, but in abbreviated form, it is an important tool for all physicians.

The present chapter which is derived from the author's teaching experience to medical students, psychiatry residents, and family physicians considers both classical and modern psychopathologic concepts. It is divided into appearance and behavior, psychomotor activity, affect and mood, speech, thinking, perceptual disturbances, orientation, attention and memory, as well as reliability, judgment and insight. Finally, common errors in mental status in clinical evaluation are discussed.

Keywords Mental status · Psychiatric history · Psychiatric interview

This chapter is devoted to the science and art of eliciting the signs and symptoms of mental disorders. The systematic perusal of these manifestations during the psychiatric interview constitutes the mental status examination, which can be viewed as analogous to physical examinations in other branches of medicine (1).

> Consider, as an example of this process, the mental examination of a 26-year-old single, male Caucasian engineering student who was brought to the hospital because of "acute sinus trouble." He had locked himself in his apartment for a week and refused to speak to anyone. When asked about his reasons for this behavior, he stated that he did not wish other people to hear the "noise emanating from my sinuses." The patient looked disheveled and had a frightened facial expression. Despite the psychotic content of his verbalizations, associations were grossly intact. Upon further questioning, he admitted that the "sinus noise" actually consisted of "voices, as if a transistor was installed up there in my head." The voices that were of the greatest concern to him argued in the third person about whether or not he was a "female." He was tremulous and restless during the interview, and on one occasion, he walked to a mirror and began to examine his facial features; with great reluctance, he admitted that he was being "transformed into a female," as the voices implied. At one point he became hostile and threatened to take legal action against a surgeon who, he believed, had "Implanted a device" into his sinuses during an operation for deviated nasal septum 8 months earlier; he added that subsequent to this operation he had intermittently experienced "foul smells" which, like his thoughts, had been "'implanted from outside." All these manifestations occurred in clear consciousness, without evidence of disorientation or memory disturbances.

To arrive at a diagnostic formulation, the examiner considers the signs and symptoms observed during the mental status examination in combination with information obtained from the psychiatric history. In this case, the diagnosis of paranoid schizophrenia was suggested by lifelong traits of seclusiveness, suspiciousness, and litigiousness; the absence of a history of substance abuse; and persistence of this clinical picture for longer than 6 months in the absence of major mood symptoms. Laboratory studies [e.g., negative urinary drug screen for stimulants and a normal sleep-deprived electroencephalogram (EEG)] were used to rule out, respectively, the remote possibility of stimulant-induced psychosis or complex partial (temporal lobe) seizures as the basis for his presenting complaints. Such physical workup to rule out somatic contributions is often a

H.S. Akiskal, M.D. (✉)
Professor and Director of International Mood Center, Department of Psychiatry, and Division of International Health and Cross-Cultural Medicine, University of California at San Diego, La Jolla, CA, USA
e-mail: hakiskal@ucsd.edu

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necessary step in psychiatric presentations with complex symptomatology, especially in patients with first psychotic breakdowns (2, 3). The presence of a positive family history for schizophrenia in a paternal cousin provided further support for a schizophrenic diagnosis.

Thus, the diagnostic process in psychiatry is analogous to that used in other branches of medicine: personal history, family history, examination, and laboratory tests constitute the essential steps. Because the raw data of psychopathology are often subjective and may elude precise characterization, the mental examination is of particular importance in psychiatry. Accurate description is difficult to obtain without careful and skillful probing during face-to-face interview. The faithful description of subjective experiences in psychiatry, known as *phenomenology*, was perfected by the German psychiatrist Karl Jaspers (4). His approach differs from that of Freudian psychodynamics, which concerns itself with the unconscious meaning and interpretation of symptoms. In contrast to the Freudians, who focused on the content of psychopathology, hypothesized to arise from early life situations and current interpersonal distortions, Jaspers believed that phenomenology—by its emphasis on the *form* of psychopathologic experiences—would eventually disclose "primary" symptoms, which are closest to the neurophysiologic substrate of the illness and which would therefore carry the greatest diagnostic weight. For instance, in the case of the engineering student, the fact that he heard voices arguing about him in the third person is more important *diagnostically* than what those voices said about him (that he was a female). The latter can variously be interpreted psychodynamically or by some other theoretical frame of reference, which pertains to the *formulation* of the case, not formal diagnosis.

A detailed mental status examination constitutes an area of psychiatric expertise, but in briefer format, it is an essential tool for all physicians. A brief mental status examination should be performed as part of the routine physical examination on all patients. When indicated, this should be followed by a more detailed mental examination.

1.1. The Importance of Signs and Symptoms in Psychiatry

Precision in the use of clinical terms to describe signs and symptoms is essential in all branches of medicine, promoting professional communication and preparing the ground for differential diagnostic workup. Imagine, for instance, what would happen if a patient with hemoptysis was erroneously described as having hematemesis. This would certainly confuse one's colleagues as to the medical status of the patient and could lead to an inappropriate series of diagnostic procedures. One can cite many other examples, such as jaundice versus pallor, ascites versus obesity, a functional versus an aortic stenosis murmur, which can all lead to difficulties in differentiation. In brief, genuine difficulties in eliciting, describing, and differentiating the myriad signs and symptoms that characterize diseases occur in all branches of medicine. Psychiatry is certainly not immune to such difficulties, but the belief—regrettably voiced by some medical educators—that differential diagnosis in psychiatry is haphazard and unproductive is both unfounded and dangerous. It is such attitudes that often lead patients with "functional" complaints to be labeled as "crocks," without the benefit of appropriate diagnostic evaluation. They may be viewed as having "imaginary" somatic complaints that waste the physician's time. The potential dangers of such attitudes can be seen in a study in the *Annals of Internal Medicine* (5), which reported that the majority of a sample of completed suicides in St. Louis were seen by physicians within 6 months before their deaths; not only was the depressive nature of their ailment missed, but sedatives, in lethal quantities, were prescribed for their complaints of disordered sleep.

Although physicians typically spend many years mastering the art and science of physical diagnosis, little attention is given in medical education to the mental status examination. Many physicians are unaware that there exist systematic rules—analogous to those used in physical diagnosis—and which can serve to assess mental status. Moreover, it is seldom recognized that the failure to distinguish, for instance, whether a patient is "sedated" or "depressed" can be as grave as the failure to distinguish between dyspepsia and angina: just as angina can be the prelude to myocardial infarction, unrecognized depression can be the prelude to jumping out the hospital window.

The mental status examination is not just common sense or an expression of humane attitudes that assist the physician in empathizing with the patient while probing his inner experiences. Good judgment in complex human situations (an uncommon form of common sense!) and an approach that considers the patient in his or her totality are not the sole prerogative of psychiatry: they are important in all branches of medicine. These attitudes merely set the stage for the practice of the clinical principles that constitute the body of scientific knowledge in any field. In psychiatry, there are established rules in the use of phenomenologic terms to arrive at diagnostic formulations that are the product of nearly 200 years of systematic clinical observation (6, 7). International consensus and standardization have now been reached on the description and clinical probing of psychopathologic experiences as exemplified in the World Health Organization development of the Schedule for Clinical Assessment in Neuropsychiatry (SCAN) (8). The SCAN covers in depth all facets of psychopathology. The Mini-Mental Status Examination (9), widely used at the bedside, is another more focused interview.

1.2. Special Problems in Psychiatric Phenomenology

Admittedly, there are many difficulties in the application of psychiatric terms and concepts. These fall into several categories.

Many psychiatric phenomena are subjective and do not easily lend themselves to objective description.

> For instance, one of the author's patients described herself as being "transformed into a pig" while looking in the mirror. Here, the patient's verbal report is the only evidence for the occurrence of this experience. It is important to record such symptoms – in the patient's exact words – to decide whether the incident is indicative of incipient schizophrenia (psychotic depersonalization in which the self changes) or primary mood disorder (a depressive delusion that one is as ugly and dirty as a pig). This patient, who had no family or personal history of mental illness, suffered from a psychotic major depressive episode. She also saw herself in a coffin and heard voices commanding her to cut her throat with a butcher knife. She recovered fully with a course of electroconvulsive therapy (ECT).

The concepts used in psychiatry are not readily susceptible to the same kinds of external validation that are used in other branches of medicine (e.g., laboratory data). Psychiatrists often rely on family history, treatment-response, and prospective course in validating diagnostic decisions made during cross-sectional examination. For instance, in the case just described, the response to ECT and the full recovery from the psychotic episode strongly favor the affective diagnosis. There has been considerable momentum in attempting to link psychopathologic events with biologic correlates (10). Although no single biologic finding has yet been accepted universally as an unambiguous marker for a specific psychiatric syndrome, several sleep laboratory and neuroendocrine indices can sometimes now be used—along with more traditional approaches—in elucidating diagnostic dilemmas (11–13). These biologic markers, then, are not meant to substitute for clinical judgment, but to supplement it in difficult differential diagnostic decisions.

These foregoing considerations pertain to the external validation of the so-called functional psychiatric syndromes. Laboratory tests are of course used in differentiating general medical and central and peripheral nervous system diseases which are known to produce psychiatric disorders from those in the absence of such ostensible etiology. Unfortunately, at this writing, despite massive and continued research efforts along the lines of genetic and brain imaging techniques, no specific laboratory tests exist for the diagnosis of common mental syndromes without known organic lesions. Psychiatric diagnosis at the present remains quintessentially a clinical endeavor based on the clinical acumen of the examiner at the bedside or in the clinic.

Mental health professionals themselves have, at times, been imprecise in the use of psychopathologic terms and concepts. This situation, however, has improved with the advent of modern pharmacotherapy and biologic psychiatry, in which syndrome-specific treatments, such as mood stabilizers, SSRIs, antipsychotics, and anxiolytics, dictate precise diagnostic evaluation and the course of illness.

Being awarded a doctorate in medicine does not automatically confer to the recipient the art of communication. Given the life-and-death nature of their endeavor, medical students—perhaps more than any other group of professional students—should endeavor to develop the proper habits of precise expression. I am not referring to literary flair—though that would be admirable—but *clarity* of prose.

1.3. Recording Signs and Symptoms in Psychiatry

Signs refer to the clinician's observations of the patient. Symptoms, on the other hand, represent the subjective complaints of the patient based on his verbal report. For instance, agitation is a sign, based on the observation of motor restlessness, pacing, pulling one's hair, and so on. Auditory hallucination is a symptom typically based on patient report. Signs assume major significance when the patient is mute, stuporous, confused, or reluctant to talk.

Whenever feasible, one should try to corroborate symptoms with other observations. There are several ways to accomplish this:

- *Recording overt behavior that is consistent with the symptom*. For instance, does the patient who reports hearing voices appear preoccupied—perhaps mumbling to himself in an attempt to answer the voices? More gravely, the patient may obey the commands given by voices. Likewise, the presence of a delusion can be inferred from behavior that results from it. For instance, a patient who believes himself to be persecuted by the Mafia may decide to move to another town.
- *Recording historical data consistent with the symptoms*. Often patients' reports suggest corollary data that can be confirmed or refuted by other information obtained from patient or significant others. For instance, in the case of a patient who reports loss of ability to derive pleasure from life (anhedonia), one may question his wife as follows: Does he indulge in his hobbies? Does he engage in sexual activities that he previously enjoyed? For the patient who complains of loss of appetite, one might inquire whether he had lost weight or whether his clothes are large on him.
- *Recording other subjective experiences correlated with the symptom*. In some situations this is indeed the best validation. For instance, the report of homosexual orientation or preoccupation can be assessed in terms of masturbatory fantasies.

In this instance, it is known that homosexual masturbatory fantasies may be more valid indicators of homosexuality than, say, incidental same-sex activity.

- *Physiologic monitoring*. In some situations, a precise physiologic measure can be recorded to substantiate a symptom. The subjective complaint of insomnia, for instance, can be measured with all-night sleep polygraphy (14). This is important because many complaints of insomnia are vague. Neurophysiologic evaluations in sleep laboratories have indeed found that some "insomniacs" actually sleep as long and consistently as people without sleep complaints. Other insomniacs manifest delayed latency to sleep and frequent awakening in the first part of the night (as is characteristic of anxiety disorders). Others manifest early appearance of the first period of rapid eye movement and frequent awakening in the middle and terminal part of sleep (as is characteristic of clinical depression). Finally, other sufferers of insomnia may exhibit specific physiologic changes that characterize specific sleep disorders such as restless leg syndrome and nocturnal myoclonus.

A cardinal rule in recording psychopathologic phenomena is to distinguish clearly those phenomena which are based on history, direct observation, or patient report from inferences that one may derive from such phenomena. For instance, the clinician should avoid describing a patient engaging in "massive projection," when what the patient said was "everyone hates me." The patient's actual report should appear in quotes in the mental status proper, while the inference of "projection" (if made plausible by other evidence) is best reserved for psychodynamic formulation (15). Thus the mental status examination should be free from speculation: it should be a record of the patient's mental condition as described by him and as observed by the clinician.

Aristotle has said that some phenomena, such as colors, can only be defined by pointing at them. This is also true of many manifestations of psychopathology that can be learned only in reference to actual patients. Hence the definitions offered in the following sections are merely a guide for a more intensive patient-based study. Moreover, this is not an exhaustive list of approaches and terms used in mental status examination. The differential diagnoses of signs and symptoms discussed throughout this introductory chapter will selectively focus on those concepts which have special diagnostic significance and which appear to be particularly problematic for trainees.

1.4. Conduct of the Mental Examination

The areas covered in the mental status examination are summarized in Table 1.1. Although flexibility is necessary to allow for special circumstances presented by individual patients, a complete psychiatric examination generally should cover all these areas and is conventionally written up (if not conducted) in the order outlined.

Patients presenting problems generally dictate the types of questions asked and the length and depth of interview. Research clinicians often conduct extensive structured interviews using specific probes for a standardized assessment of individual signs and symptoms. Practicing clinicians have traditionally conducted more or less unstructured interviews that provide for flexibility to tailor questions to the particular situation of the individual patient. Current experience indicates that when major mental illness is suspected, much can be gained by combining the virtues of these two approaches in a semistructured format. This way

TABLE 1.1. Mental status examination outline.

Appearance and behavior
Attire, grooming, appears stated age?, posture, facial expression, eye contact
Attitude toward interviewer
Friendly, cooperative, seductive, ambivalent, hostile
Psychomotor activity
Normal, retarded, accelerated, agitated, catatonic symptoms
Affect and mood (*emotional state*)
Euthymic, irritable, anxious, labile, inappropriate, blunted or flat, depressed, elated
Speech and thinking
Process or form: coherent, circumstantial, pressure of speech, flight of ideas, derailment (loose associations)
Content: phobias, obsessions, compulsions, delusions
Specific speech disorders: echolalia, perseveration, mutism, aphonia, aphasia
Perceptual disturbances
Illusions, hallucinations, depersonalization, derealization
Orientation
Time, place, person, situation
Attention (*concentration*) *and memory*
Digits forward and backward, serial 7, street address, recall of three objects, amnesia
Intelligence
Abstraction, vocabulary, global clinical impression of IQ
Reliability, judgment, and insight

one would conduct a full examination to inquire about areas that an unstructured interview could easily miss while at the same time providing flexibility to follow the patient's leads and to frame the questions as best understood by that patient. When conducting an interview, beginning students should have available for quick reference an outline of the mental status examination, as well as the specific signs and symptoms most relevant to the differential diagnosis at hand. A pocket copy of the "mini-DSM-IV-TR" (16) is useful for this purpose; another useful guide is Goodwin and Guze's *Psychiatric Diagnosis* (17).

It is not necessary to conduct all parts of the interview with the same depth on all patients. For instance, one need not directly check the orientation, vocabulary, and calculating ability of a moderately anxious young university professor who appears to be in good contact. Nor is it necessary to inquire extensively about bizarre psychotic experience when interviewing a diabetic patient who presents with the chief complaint of difficulty in attaining erections. Experience teaches one when such shortcuts can be made. The examiner must at times forego inquiry into a given area out of consideration for the patient, who may be unwilling or too uncomfortable to talk about certain topics; if the omitted area is of major significance for differential diagnosis, one should endeavor to obtain collateral information from significant others or return to questioning the patient at a later time, using a more indirect approach. There are situations in which one should conduct the mental status in multiple brief encounters, as in the case of extremely disturbed, violent, psychotic, or semistuporous patients, attempting to glean the optimal amount of information necessary for a tentative diagnosis.

1.5. Areas of the Mental Status

The mental status typically begins with a statement about the setting in which the examination was conducted (e.g., inpatient or outpatient, private or public institution) and the purpose for which it was done (e.g., initial evaluation for outpatient treatment, disability determination, consultation for another physician). It typically follows a careful review of all existing records and proceeds with the areas described below.

1.5.1. Appearance and Behavior

Although this is the first section of the mental examination, relevant data are gathered throughout the interview process. Attire, posture, facial expression, and the level of grooming are described in such a way that the person reading the narration can visualize the patient's physical appearance at the time of the examination. It is important to note any obvious physical signs or deformities that point toward medical disease. The chronically ill and those experiencing severe depression may look older than stated age; by contrast, hypomanic, histrionic, and hebephrenic individuals may look younger. Poor eye contact may indicate shame, embarrassment, anxiety, social anxiety, or paranoid traits. In some cases, little will be revealed in this section beyond the fact that the patient's physical appearance was unremarkable compared with other individuals of same age, educational level, and socioeconomic status. In other instances, the general observation may provide important clues about the patient's personality, mood, thought, awareness of social conventions, and ability to function adequately within society.

1.5.2. Attitude Toward the Interviewer

The patient's attitude toward the interviewer is often evident without specific inquiry, simply by ongoing observing of the patient throughout the interview. Some patients relate easily, are open and cooperative, and reveal plenty of information without much probing. Others may be reticent, guarded, or even suspicious, too embarrassed, unwilling, or frightened to share personal experiences. Some may be overtly hostile, even attempting to embarrass or humiliate the examiner; in the extreme, the patient may be uncommunicative or openly belligerent. Some patients are obsequious, trying to flatter the examiner, emphasizing how competent he is compared with all previous doctors, who "do not seem to care." Others may display *ambivalence*, a term that refers to the simultaneous presence of "incompatible" emotions (positive and negative). Still others may be overtly seductive. Clinical experience teaches the clinician how to interview these different kinds of patients. The two extremes of aggressive and seductive behavior represent the greatest challenge for clinical interviewers. Faced with such behaviors, the interviewer must set limits and maintain objectivity without losing empathy.

1.5.3. Psychomotor Activity

Psychomotor activity refers to physical activity as it relates to psychological functioning. A patient who displays "psychomotor agitation" moves around constantly, cannot sit still, and often shows pressure to talk. One may observe hand wringing, shuffling of feet, crossing and uncrossing of knees, picking on scabs, scratching, nail biting, hair twisting, and even hair pulling. One

must contrast such purposeless physical restlessness with the more patterned psychomotor acceleration, in which the patient is extremely "busy," engages in many activities, talks incessantly by jumping from topic to topic, and experiences rapid thought progression. In the extreme, both agitation and acceleration may lead to frenzied activity that can be debilitating. In fact, before the availability of electroconvulsive and neuroleptic treatments, some of these patients died of sheer exhaustion. In other patients, one observes psychomotor retardation, in which there is a general slowing of movement, speech, and thought progression. Here, the patient may sit in a slumped, often frozen posture; speech is slow, monosyllabic, and of low pitch, accompanied by few gestures; and facial expression is either sad or blank. For such patients, talking may seem to be an effort, and latency of response to questions is typically prolonged. In some conditions, such as mixed states of affective psychosis, psychomotor agitation and retardation can be present, i.e., physical slowing with racing thoughts simultaneously; these patients are often suicidal (18). Abnormal psychomotor activity on repeated examination is usually indicative of a major psychiatric disorder. Quantitative rating of psychomotor function is now possible through the use of a reliable scale developed by Widlöcher and his team at the Salpetrière Hospital in France (19). Despite proposals to develop physiologic measures of speech pause time and abnormalities of facial expression of emotions (20), this area still very much relies on qualitative judgments made by experienced clinicians. In other words, there is no objective test to determine whether the facial expression of a patient is one of fear, depression, anger, or elation (21). Darwin (22) wrote extensively about the evolutionary significance of emotions. His book, recently reprinted, remains the classic on the topic (22).

Other forms of psychomotor disturbances that occur in psychotic states include "posturing," "stereotyped movements," "mannerisms," "negativism" (doing the opposite of what is requested), *echopraxia* (imitating the movements of another person), and "waxy flexibility" (maintaining certain awkward positions despite apparent discomfort). In the extreme, such manifestations may progress to *stupor*, which represents an extreme degree of psychomotor retardation and mutism combined. The condition is sometimes observed on the battlefront or in civilian catastrophes, where the victim may be "paralyzed by fear." In the absence of such history, organic contributions should be excluded by EEG, various brain imaging techniques, lumbar puncture, and other laboratory tests. Once this is done, intravenous amytal may help in differentiating depressive from schizophrenic stupor; the schizophrenic patient will momentarily come out of his state of inactive *mutism*, and express delusional thoughts, for example, that he dare not move because his weight "would tilt the balance of the earth and bring the end of the world." The two conditions may be further distinguished clinically by the presence of urinary incontinence, catalepsy (increased muscle tension), and expressionless *facies*, all of which are more suggestive of catatonic schizophrenia than of depression.

1.5.4. Affect and Mood

Affect is the prevailing emotional tone during the interview, as observed by the clinician. One must describe whether the patient exhibits an appropriate range of affect, which varies with the theme of the conversation and may include fear, sadness, and joy. In the case of marked disparity between affect and thought content, one speaks of inappropriate or "incongruent affect." Other commonly observed disturbances of affect include tension (or inability to relax), panic (a crescendo increase in fear), anger (a predominantly argumentative or hostile stance), "lability" (rapid shifts from happiness to sadness, often accompanied by giggling, laughing, or, conversely, sobbing and weeping), and "blunting" or flattening (minimal display of emotion, with little variation in facial expression). In addition to the observed disturbances of affect, the clinician also must record the mood, or subjective feeling state, reported by the patient over the preceding several days or weeks. The most common moods reported by patients are depression (i.e., feeling in "low spirits" or "down in the dumps") and anxiety, a feeling of apprehension whose source remains undefined. When irritability is the prevailing mood, the patient may report having a "short fuse." In "euphoria," the mood is one of extreme elation and jubilation that is not justified by objective circumstances. These self-reports will not necessarily coincide with the observed affect. For instance, some patients may have a gloomy, downcast expression, yet vigorously deny experiencing depressed mood; conversely, patients who do not show prominent signs of emotional distress may report a pervasive gloom. Such lack of concordance between subjective report of mood and observable affect and behavior is not uncommon in both normal and psychopathologic states (23). In the absence of specific disturbance in affect or mood, the patient is described as "euthymic."

1.5.5. Speech and Thought

In this section the examiner describes the patient's verbal communication and its disturbances. *Thought form* (or thought process) refers to how ideas (or associations) are put together in an observed sample of speech and in what sequence and speed. A patient exhibiting no abnormality in the formal aspect of thought is said to have intact associations, coherent thought that is clear, logical, and easy to follow and understand. In "circumstantiality," there is a tendency to answer questions in terms of long-winded details. In "pressure of speech," the patient seems to be compelled to talk, while in "flight of ideas," thoughts actu-

ally race ahead of the patient's ability to communicate them; he skips from one idea or theme to another, and ideas may be connected by rhymes or puns ("clang association"), as shown in this address made by a patient to the psychiatrist in chief during the morning round: "Let me part soon … to the moon … moonshine is for lovers … the cure for lovers' heart … the lure of poets … the doors of perception … a magnificent conception … on! on! Let me conquer the moon."

This form of thought is most characteristic of mania and tends to be overinclusive, with difficulty in excluding irrelevant, extraneous details from the association. In the extreme, it may be hard to draw the line between manic flight of ideas and schizophrenic derailment (literally, "off the track"), in which it is impossible for the observer to glean any logical sequence from the patient's speech. Patients with the latter degree of "loosening of associations" sometimes invent new words that have private meanings ("neologisms"). Associative slippage also may manifest in general vagueness of thinking, which is not grossly incoherent but conveys little information, even though many words may have been used. This disturbance, known as "poverty of thought" (24), is a major diagnostic sign of schizophrenia, when known organic mental disorders have been ruled out. Here is a sample from a letter a high school student wrote to the psychiatrist in response to the question why he was in the hospital: "I often contemplate—it is a general stance of the world—it is a tendency which varies from time to time—it defines things more than others—it is in the nature of habit—this is what I would like to say to explain everything."

Bleuler (25) coined the term "autism" to refer to the self-absorption that he believed characterized schizophrenic thought, feeling, and behavior (25). Thinking that is governed by inner drives and a "private logic" is therefore known as autistic thinking; "dereistic thinking" is a synonym for it. Current evidence indicates that such thinking may actually reflect, in some cases, reactive reduction of left cerebral density (26).

"*Echolalia*," most commonly observed in catatonia, is the irrelevant, sometimes playful, repeating of words used by the interviewer (e.g., "What day is today?" "Today"). In "perseveration," also seen in catatonia, as well as in chronic organic mental disorders, the patient adheres to the same concept or words and appears unable to proceed to others. "Thought block" refers to the sudden arrest of thought in the middle of a sentence, often followed, after a momentary pause, with a new and unrelated thought. When mild, this experience may be caused by exhaustion, anxiety, or depression; severer degrees are seen in schizophrenia, where they may be the observable counterpart of the subjective experience of thought withdrawal. *Mutism* consists of the loss of speech and can be intentional in origin (as part of a dramatic cluster personality disorder) and limited to interactions with certain people (elective mutism) or involuntary (as part of catatonia or midline lesions of the brain). In *aphasia*, owing to dominant temporal lobe lesions, the patient has a specific memory disorder for words and language; even when unable to talk, the patient usually attempts to communicate by other methods. In *dysphonia*, the patient loses his voice and cannot raise it beyond a whisper, which, in the extreme, can proceed to aphonia; here, in contrast to mutism, one can observe lip movements or nonverbal attempts to communicate. Unless based on laryngeal pathology or excessive use (i.e., as in teachers) or abuse of vocal cords (as seen in voluble manics), these deficits in phonation are almost always due to a conversion disorder, representing, for example, a compromise in an adolescent who feels conflicted between lying and telling her parents the truth about sexual behavior of which they would strongly disapprove.

Common abnormalities of *thought content* include obsessions (repetitive ideas, images, or impulses that intrude into consciousness unwanted, yet patients are aware that these thoughts are their own), compulsions (irresistible urges to engage in apparently meaningless acts), and phobias (irrational fears unjustified by objective circumstances). Phobias are usually categorized by the circumstances eliciting them, such as social phobia (a common form of which consists of fear of facing a group in a lecture situation), agoraphobia (fear of going out alone in public places), acrophobia (fear of heights), etc.

Two obsessions that commonly torment neurotic patients are the unwanted idea that one might inadvertently harm or kill loved ones and that one could be contaminated by germs, dirt, excreta, or other undesirable elements. The latter obsession is typically associated with cleaning compulsions or rituals to rid oneself of such elements. The unwanted idea (obsession) that one might inadvertently hurt loved ones does not ordinarily lead to taking action; instead, it may be associated with the ritual of hiding away knives, scissors, other sharp objects, etc. Thus obsessions with aggressive content should be distinguished from homicidal ideation or threats, which do carry some likelihood of being carried out. The clinician must likewise distinguish between an obsession with self-injury content and suicidal ideation. The former refers to the tormenting thought that one might, contrary to one's value system, hurt or kill oneself. However, in other patients, the pain of depression can be of such a magnitude that the normal barriers that prevent one from taking one's life do break down, and thus suicidal thoughts can lead to suicidal action; suicidal ideation is a particularly ominous symptom if associated with loss of hope for the future (hopelessness). Such patients should be carefully monitored to prevent suicide (27). Therefore, *the clinician should always inquire about suicidal ideation and suicidal plans (as well as current and past attempts and their outcome)*; the notion that one thereby inadvertently "puts thoughts into the patient's head" is unfounded; on the contrary, patients are typically relieved that the physician is aware of their mental suffering and could provide appropriate measures to terminate it. It is also important to realize that not all depressed patients actively contemplate suicide; instead, this propensity may be expressed more passively as a general feeling that life holds little meaning for them (tedium vitae) and that they would prefer not to wake up in the morning, or that they would welcome a fatal disease or an accident. It is incumbent upon the psychiatric examiner to explore such possibilities with circumspection and sensitivity.

"Delusions" are common abnormalities of thought content among psychotic patients. They are defined as false beliefs that are unshakable and idiosyncratic to the individual. Thus the beliefs of a delusional patient cannot be typically undone by logical arguments to the contrary, as illustrated in the following vignette:

> An African-American female inpatient, admitted to an emergency psychiatric service, believed that she was Jesus Christ. When questioned by a nursing trainee how this was possible, given that Christ was male, white, and Jewish, the patient responded with a smile: "The Bible is wrong." The examiner in this instance was lucky to elicit a mere smile; delusional beliefs are often associated with more vehement affect. Therefore, they should be probed with the requisite tact and sensitivity on the part of the examiner, especially when they involve race, gender, and religion.

It is also important to keep in mind that the idiosyncratic nature of delusional beliefs means that they are *not shared by members of the same culture or subculture*. For instance, the belief that one is sexually "voodooed" and will not regain one's potency until the spell is lifted is not necessarily delusional; neither are beliefs in unusual health practices and folk remedies. The decision of whether one is dealing with a culturally accepted phenomenon must be based on a thorough knowledge of a given culture or subculture. To complicate matters, in cultures where voodoo and witchcraft are part of daily life, delusions may sometimes represent pathologic elaborations of such beliefs. The definitive test is whether an unusual belief is shared by members of the patient's subculture. Delusions also must be differentiated from "overvalued ideas," which are fanatically maintained notions, such as the superiority of one sex, nation, or race over others, and while not necessarily an indication of clinical pathology, such ideas may, in the extreme, suggest the diagnosis of a personality disorder described by the German psychiatrist Kurt Schneider as a "fanatical psychopathy" (28).

Delusions are categorized as "primary" or "secondary." Primary delusions cannot be understood in terms of other psychological processes. The most common examples of these are represented by Schneider's first-rank symptoms (29), which consist of externally imposed influences in the spheres of thought ("thought insertion"), emotion, and somatic function ("passivity feelings"), as well as experiences of "thought withdrawal" and "thought broadcasting"; hence they are also known as delusions of control or delusions of influence. Primary delusions may arise in the setting of what is termed "delusional mood," in which the patient is gradually losing his grasp of reality: neutral percepts may suddenly acquire special personal or revelatory significance of delusional proportion (e.g., a red car being seen as an indicator of imminent invasion by communist forces). This two-stage phenomenon, known as "delusional perception," is also considered a first-rank symptom. Although one or two Schneiderian symptoms may be seen in severely psychotic affective—especially manic—patients (30, 31), the presence of a large number of such symptoms usually points toward schizophrenia (32, 33), provided that stimulant-induced psychosis, complex partial (temporal lobe) seizures, and alcoholic hallucinosis are excluded.

Secondary delusions derive from other psychopathologic experiences and occur in a variety of psychiatric disorders. Delusions may be secondary to:

- Hallucinations—the patient hears the voice of his deceased mother and concludes that he must be dead too.
- Other delusions—the patient believes that he is being persecuted by others, may decide that he must be the messiah.
- Impaired memory—a patient with general paresis of the insane (tertiary syphilis) who, unable to remember where she had placed her purse, repeatedly called the police to report that her neighbors were robbing her.
- Morbid affective states—These are sometimes referred to as *affective delusions* and arise from the prevailing mood—usually depression—and the associated guilt, low self-esteem, and insecurity (33).

Delusions can take the form of delusions of guilt or sinfulness (the belief that one has committed an unpardonable act), delusions of jealousy (false belief in infidelity of spouse or lover), hypochondriacal or somatic delusions (i.e., delusions of ill-health), nihilistic delusions (the belief that parts of one's body are missing), and delusions of poverty (the belief that one has lost all means and family members will starve).

Other delusions secondary to affective states include *delusions of reference* (the idea that one is being observed, talked about, laughed at, etc.), *erotomania* (in which the patient believes that a famous person is in love with him or her), and *grandiose delusions* (belief that one has unusual talents or powers or that one has the identity of a famous person). Although erotomania and grandiose delusions often arise in the setting of expansive mood, one can usually find clinical evidence for underlying low self-esteem or depression. Delusions of reference can occur in affective, schizophrenic, as well as organic psychoses. In what is termed *delusions of assistance*, the patient believes oneself to be the object of benevolence from others or supernatural powers; for example, a manic woman, who had run away from her ex-husband's harassment, stated that chariots were being sent to transport her and her children to heaven. In the more common persecutory delusions, the patient believes oneself to be the target of malevolent action; this may be due to the conviction that one is somehow guilty and deserves punishment, or it may result from a grandiose self-concept; in other cases, the patient may be misattributing his hostile impulses to his presumed persecutors.

1.5.6. Perceptual Disturbances

The simplest form of perceptual aberration is represented by an *illusion*, often in the visual sphere, in which real stimuli are mistaken for something else (e.g., a belt for a snake in a dimly lit room). Such misinterpretation can be secondary to exhaustion, anxiety, altered states of consciousness, delirium, or a functional psychosis.

Hallucination, a more serious perceptual disturbance, consists—in Esquirol's definition—of a perception without external stimulus (34) (e.g., hearing voices when nobody is around, seeing things that are not there, or perceiving unusual odors and tastes). In synesthesia, observed in psychedelic intoxication, the perceptual disturbances are in more than one sensory modality, and the subject "hears" colors, "smells" music, and so on. For example, Baudelaire, the French poet whose drug experimentation was well known, wrote about the color of vowels: "A noir, E blanc, I rouge, U vert, O bleu" (i.e., A = black, E = white, I = red, U = green, and O = blue).

Auditory hallucinations are classified as either elementary (noises) versus complete (voices or words). They are commonly reported by schizophrenic patients, but also occur in organic mental disorders and drug intoxication or withdrawal. Some patients in the initial stages of a psychotic breakdown report hearing their own "thoughts spoken aloud" (*écho de pensée*); at a later stage, voices lose their connection with the person and appear to be coming from outside, making a "running commentary" on the patient's behavior or arguing about him in the third person. These are all special categories of hallucinatory phenomena included in Schneider's list of *first-rank symptoms* (29). They occur in a variety of psychotic disorders, but when they are extremely pronounced or continuous, they suggest schizophrenia. Typically, Schneiderian hallucinations are considered to be "mood-incongruent" in that they have no plausible link to the patient's state of mood. Other hallucinations also can be "mood-congruent"; these are observed in the affective psychoses, in which voices make derogatory statements about the patient, usually in the second person ("You are a jerk") or give self-destructive commands ("Slit your throat"). Perceptual disturbances that occur in affective illness tend to be transient and typically occur at the depth or height of an affective episode or during the unstable neurophysiologic transition (mixed state) from depression to mania. They also can arise from the exhaustion, dehydration, or superimposed drug or alcohol abuse that often complicates affective disorders; these complications explain in part why mood-incongruent psychotic experiences are occasionally seen in otherwise classic affective psychoses (33).

Visual hallucinations are most characteristic of organic mental disorders, especially acute delirious states. Sometimes they are "Lilliputian" (less than life-size); they may coexist with auditory hallucinations and can be frightening. Visual phenomena associated with psychedelic drugs can be pleasant or frightening, depending on mental set. Visual hallucinations, sometimes elicited from manic patients, are not characteristic of schizophrenia but can occur in normal grief (visions of a dead relative), in depressive psychoses (e.g., seeing oneself in one's casket), and in brief reactive psychoses observed in abnormal personalities. "Hypnagogic" and "hypnopompic" hallucinations are visual experiences that occur in twilight state between sleep and wakefulness, occurring, respectively, when falling asleep and waking up. Although their occasional occurrence is normal, repeated experiences, especially when associated with sleep paralysis and sudden loss of muscle tone under emotional arousal (cataplexy), are cardinal manifestations of narcolepsy, representing rapid eye movement intrusions into consciousness. Other circumstances that can provoke visual hallucinosis include sensory deprivation (e.g., after cataract surgery), delirium, and other organic mental disorders (35). Histrionic personalities may give flamboyant accounts of "perceiving" objects or events that fit their fantasies. All these manifestations must be distinguished from perceptual disturbances, in which objects may seem to get larger or closer (macropsia) or smaller and recede into space (micropsia), which are special forms of illusory phenomena that occur in retinal detachment, disorders of accommodation, posterior temporal lesions, and psychedelic drug intoxication. Finally, psychedelic drugs can produce impression of extremely vivid colors with geometric patterns known as "kaleidoscopic hallucinations."

Olfactory hallucinations may be difficult to distinguish from illusions. For example, a woman with low self-esteem might be preoccupied with vaginal odor and might misinterpret neutral gestures made by other people as indicative of olfactory disgust. In complex partial seizures of temporal lobe origin, hallucinations of burning paint or rubber present as auras.

Haptic hallucinations (hallucinations of touch) are usually experienced as insects crawling on one's skin (known as "formication") and characteristically occur in cocaine intoxication, amphetamine psychosis, and delirium tremens owing to alcohol or sedative-hypnotic withdrawal. In schizophrenic disorders, they may take such bizarre forms as orgasms produced by invisible objects or creatures. Tactile hallucinations must be distinguished from extreme tactile sensitivity (hyperesthesia) and diminished sensitivity (hypesthesia), both of which can occur in peripheral nerve disease as well as in conversion disorders.

Vestibular hallucinations (e.g., those of flying) are seen most commonly in organic states, such as delirium tremens and LSD psychosis, and may result in serious injuries when, for example, the subject attempts to fly off a roof. In hallucinations of presence, most commonly reported by schizophrenic, histrionic, or delirious patients, the subject senses the presence of another person or creature who remains invisible. In extracampine hallucinations, the patient sees objects outside the sensory field (e.g., behind his head), whereas in *autoscopy*, the patient visualizes himself projected into space. The latter phenomenon, which can occur in organic, conversion, depressive, and schizophrenic disorders, is also known as "Doppelganger," or seeing one's double, and is skillfully portrayed in Dostoevski's novel, *The Double*.

Other perceptual disturbances that cannot be classified easily into specific sensory modalities include depersonalization (the uncanny feeling that one has changed), derealization (the feeling that the environment has changed), *déjà vu* (a sense of

familiarity with a new perception), and *déjà entendu* (the feeling that a new auditory perception has been experienced before). As isolated findings, these can occur in normal people who are anxious, tired, or sleepy, but repeated experiences along these lines indicate the following differential diagnoses (36): complex partial seizures, panic disorder, schizophreniform psychosis, hysterical dissociation, and psychedelic intoxication.

1.5.7. Orientation

In this section the clinician records whether the patient knows who he or she is (orientation to person), the place of the interview (orientation to place), the purpose for being there and the nature of the interview (orientation to situation), and, finally, what date and time of day it is (orientation to time). One who is orientated in all spheres is considered to have a "clear sensorium." Patients with affective and schizophrenic psychoses are not typically disoriented (although, because of apathy, they may fail to keep track of daily routines), whereas patients who suffer from organic mental disorders are characteristically disoriented in some or all the above areas. In acute brain disease, patients often show remarkable fluctuation in orientation depending on time of day, with worsening disorientation at night. With increasing severity of brain impairment, the patient is totally confused as to orientation, and the sensorium may be clouded at all times to such an extent that in the very extreme he may lapse into an organic stupor.

1.5.8. Attention (Concentration) and Memory

The patient who shows deficits in attention or concentration is often unable to filter relevant from irrelevant stimuli as they pertain to the interview material and thus may be easily distracted by the TV, telephone, and other background stimuli. A patient with milder disorder may be able to achieve the attention required for a successful interview but may complain that his or her mind is "not working." Care must be taken to distinguish between deficits in attention, which are involuntary, and lack of cooperation; an example of the latter would be a patient who whistles instead of answering questions that are being posed. Attention and concentration are usually tested by digits forward and digits backward ("Can you repeat 7248 forward? Can you repeat it backward?"). A related test is serial sevens (i.e., subtracting 7 from 100 and from each successive remainder); in using this test, the observer needs to make some allowance for educational background; thus, one might elect to start with "serial threes."

Deficits in memory are conveniently grouped into four kinds: (1) immediate, when the patient cannot even register things one has just been told, (2) short-term, when one cannot retain information for 5 minutes or so, (3) recent, unable to recall the events of the past months or years, and (4) long-term, or remote, unable to recollect what took place many years ago. Documented deficits in immediate recall suggest serious acute brain impairment or stupor. Less severe brain insults tend to spare registration but can lead to deficits in short-term memory, which can be assessed by asking the patient to remember a street address or three unrelated items (e.g., "17, yellow, chair") in 5–7 minutes, after making sure that the patient fully understands the items to be remembered. Recent memory is most likely to be compromised by chronic organic impairment; its intactness can be tested by asking the patient about verifiable recent events in one's life or current events. Remote memory is usually spared in the early course of dementing diseases, but at later stages, it may be impaired to such an extent that the patient may not recognize his or her own children. This is best tested by asking about several past historical events that someone with the patient's social background and intelligence can reasonably be expected to be familiar with.

Disturbances in attention, concentration, and memory are most characteristic of organic mental disorders, yet schizophreniform and acute affective psychoses also may exhibit *reversible* abnormalities in these functions. Although it is customary to use the term pseudodementia to refer to this phenomenon, it appears that reversible neurophysiologic derangements underlying these psychotic illnesses may well be responsible for the observed cognitive deficits (37). Finally, memory disturbances also can result from a combination of organic insults (e.g., head trauma) and emotional causes (e.g., hysterical dissociation) that could lead to amnesia for events before ("retrograde") or after ("anterograde") the injury. In general, the more psychogenic in origin, the more circumscribed is the amnesia, and the more organic, the more global. Retrograde amnesia for autobiographic events for variable periods can also occur after a course of electroconvulsive therapy.

It is beyond the scope of this chapter to consider more formal neurocognitive testing which neuropsychologists undertake in various localizing and diffuse brain diseases.

1.5.9. Intelligence

Intelligence can be indirectly inferred from the patient's overall intellectual performance during the mental status examination. If deficits are grossly apparent, historical information should be used to decide whether they have always been present (intellectual subnormality) or developed after a certain age (intellectual impairment). Intelligence is commonly assessed by testing for abstracting ability. To accomplish this, one inquires about similarities, going from simpler comparisons ("How are an air-

plane and a car alike?") to more difficult ones ("A painting and a poem?"). The examiner also must pay special attention to the patient's vocabulary. Vocabulary and performance on similarities testing depend not only on the patient's intellectual capacity but also on his age, social background, and educational level. For instance, the presence of a good vocabulary and abstracting ability, despite a third-grade education, indicates above-average intelligence. If vocabulary and abstracting ability are poor, allowance should be made for social deprivation. In the absence of such factors, and especially if the patient has a college education, the examiner must consider the possibility of intellectual impairment owing to an organic mental disorder.

Classically, organic mental disorders have been described as involving changes in orientation, attention, memory, and intelligence. When profound, such changes provide clinical evidence for an underlying somatic disease. However, as indicated, subtle yet measurable deficits in these mental faculties often accompany the so-called functional psychiatric disorders, and such data point to underlying disturbances in cerebral structures involved with these faculties, the precise nature of which continues to elude psychiatric research. The clinician also must keep in mind the not uncommon occurrence of moderate to severe subcortical pathology or disease with relatively intact intellectual function, manifesting instead in profound alterations in perception, mood, and psychomotor behavior; delusions, obsessions, phobias, depersonalization, derealization, and related bizarre psychopathologic disturbances often accompany such disease (3, 38).

1.5.10. Reliability, Judgment, and Insight

Every mental status examination should have a statement regarding the extent to which the patient's report of his or her experiences and behavior is to be considered reliable. This assessment is largely an aggregate based on an estimate of the patient's intellectual ability, honesty, attention to detail, and motivation. Sociopathic and histrionic individuals are notoriously unreliable. "Retrospective falsification," commonly observed in such patients, consists of distortion of real past experiences to conform to present emotional needs; at other times, they may lie to avoid personal responsibilities. A related type of unreliability is "pseudologia fantastica," expansive storytelling such that the individual is unable to discern which of one's statements are true and which are false. Psychotic patients and those with organic mental disorders also tend to be unreliable informants; here one sometimes observes "confabulation," a spontaneous fabrication of responses to fill in memory gaps.

Judgment refers to the patient's ability to evaluate the proper course of action in difficult situations and is traditionally tested by asking what one would do if one were the first to observe smoke in a movie theater. The patient's history will often give clues as to whether he or she generally has good or poor judgment. Disturbances in judgment can be circumscribed to one or more areas (e.g., money, attire, sexual conduct), leaving other areas, such as maternal role, intact. "Insight" pertains to a more complex form of judgment regarding the patient's awareness of his or her emotional state, its causes, its severity, and its impact on significant others. Psychotic patients, especially in mania, notoriously lack insight and are often unaware of the painful consequences of their spending sprees and sexual promiscuity, which explains in part their frequent lack of cooperation with treatment regimens.

1.6. Common Errors in Mental Status Examination

Eugen Bleuler's work on schizophrenia (25) continues to exert a major influence in the description and differential diagnosis of schizophrenic manifestations. Bleuler believed that disturbances in associations, affect, ambivalence, and autism characterized this group of disorders. His ideas were, unfortunately, accepted before being empirically tested, leading to much confusion in mental status evaluations. This is particularly true for disturbance in affect (39) and associations (24).

1.6.1. Disturbances in Affect

The examiner must distinguish between flat and depressed affect, which occur in disorders that seldom intersect (i.e., chronic schizophrenia versus primary mood disorder). Shallow, blunted, and flat affect refer to increasing degrees of emotional impoverishment—often accompanied by a subjective feeling that one cannot experience emotions, a classical disturbance of schizophrenia. By contrast, depression is a painful affect, what William James termed a *psychical neuralgia* (40).

Depressed patients given antipsychotics, particularly classical neuroleptics, usually for agitation, may appear to have flat or blunted affect. This is seldom observed nowadays with the advent of the atypical antipsychotics.

Many depressed patients also experience anhedonia, best described by Shakespeare: "How weary, stale, flat, and unprofitable/Seem to me all the uses of this world" (Hamlet, Act I, Scene 11). Diagnostic difficulties arise in "severe" depression, where the anhedonia may progress to a pervasive sense of emptiness, often accompanied by the inability to feel normal emotions; such patients may feel "dead inside" and see the world around them as lifeless. Differential diagnosis can be accomplished as

follows: First, the facial expression of the chronic schizophrenic individual is typically vacuous, whereas that of the clinically depressed person is typically one of pain, gloom, and dejection. Second, those with schizophrenia tend to produce, in the observer, a cold feeling and an inability to empathize (the so-called praecox feeling), whereas the depressives' dejection and pain are usually communicated in such a way that the interviewer can empathize with them. Admittedly, this is a subjective criterion, but it is quite useful in the hands of experienced clinicians.

Labile affect (which changes quickly, often from one extreme to the other) must be distinguished from incongruent affect (which is inappropriate to the thought content or the context). Labile and incongruent affects should both be differentiated from "affective incontinence," in which the patient laughs or cries for long periods with little or no provocation. Lability is encountered in the dramatic cluster of personality disorders; in mixed states of manic-depressive illness, where there are rapid shifts from elation to irritability to depression; and in acute organic brain disease, where the affect can quickly change from anxiety to terror to panic. Inappropriate affect (e.g., laughing while relating the gory details of a natural disaster) should raise the suspicion of schizophrenia. Emotional incontinence suggests organic states, such as arteriosclerotic dementia and multiple sclerosis.

Euphoria and elation, although characteristic of manic states, also can occur in organic mental disorders, such as general paresis of the insane and multiple sclerosis. The euphoria seen in mania has a warmth that is communicated to the observer (although manic patients especially when crossed, can be irritable, hostile, and obnoxious); the interviewer should avoid direct confrontation with manic patients. A type of euphoria characteristic of chronic schizophrenia and frontal lobe lesions, known as *Witzelsucht*, consists of the patient relating silly jokes; these lack the empathic contagiousness of the humor of bipolar patients.

La belle indifference should be differentiated from apathy. In the former condition—observed in conversion reactions—the patient exhibits lack of concern or even smiles in the face of reported disability. Apathy, on the other hand, seen in many chronic psychiatric patients because of their overall dismal situation, is a feeling akin to or associated with general demoralization.

1.6.2. Disturbances in Thinking

Unfortunately, "thought disorder" is often involved rather loosely to refer to both formal thought disorder and delusional content. For the sake of clarity, the unqualified use of the phrase "thought disorder" should be discarded from psychiatric communication. Even the designation "formal thought disorder" covers too wide a territory. It should always be made clear whether one is referring to derailment or loose associations, flight of ideas, or circumstantiality. The presence of a delusion cannot be considered evidence of underlying formal thought disorder because, as noted previously, delusions can be secondary to affective, perceptual, and memory disturbances. We consider below several of these issues critical for a competent mental status exam.

"Derailment" refers to a disorder in associations whereby different thoughts are dissociated, disconnected, or rambling. If mild, it leaves the impression of "vagueness"; if the patient makes no sense at all, it is referred to as "word salad." The phrase "loose associations" is used for an intermediate degree of severity, wherein one finds fragmented thoughts that do not seem to follow Aristotelian logic but may nevertheless have an inner, private (autistic) logic of their own. The "incoherence" that one observes in the thinking of organic patients is qualitatively distinct from the loose associations of the schizophrenic patient in that it lacks symbolism and autistic quality; however, in severe cases of schizophrenia, this distinction may be difficult to make. *Vorbeireden*, or talking past the point, also should be differentiated from incoherence. In *vorbeireden*, which occurs in the *Ganser syndrome*, the patient gives obvious indication that he has understood the question yet deliberately provides "approximate" answers.

> For instance, a patient examined in 1977, when asked who the president was, replied, "Jerry Carter", and when asked who was president before him, he replied, "Jimmy Ford."

The Ganser syndrome seen among prisoners is best understood in terms of conscious and unconscious reasons for appearing psychotic or demented; hence it is also referred to as "hysterical pseudodementia." To complicate matters, adolescent schizophrenic patients may find approximate answers amusing and may respond to an entire interview with a series of approximate answers; such patients may therefore appear to exhibit hysterical pseudodementia, but in reality, they have a hysterical "pseudopseudodementia."

It is often erroneously assumed that inability to abstract on testing of similarities or proverbs (i.e., "concrete thinking") has major diagnostic importance in schizophrenia. There is little scientific rationale for this belief. Concreteness correlates best with poor intellectual endowment, cultural impoverishment, and organic brain disease. Because all three of these factors not infrequently coexist with schizophrenia, to that extent, schizophrenic patients will have impaired ability in abstraction. The major value of testing abstraction in schizophrenia lies in the patient's tendency to give highly idiosyncratic and bizarre answers to proverb and similarities testing.

"Pressure of speech," usually seen in agitated depression, refers to patients who feel pressured to talk and usually cannot be stopped. "Flight of ideas," a major diagnostic sign of mania, refers to a type of overproductivity wherein the patient rapidly skips from one idea or theme to another, often by resorting to rhyming or punning, but without totally abandoning logic. Pressure of speech and flight of ideas both should be distinguished from loose associations that do not follow Aristotelian logic. "Circumstantiality" is the unnecessary elaboration of detail and is seen in dullards (borderline IQ), pedantic obsessionals, and patients with severe somatization disorder, but in severe degree, it may be difficult to differentiate from schizophrenic looseness.

The clinician must note that in some manic patients examined formally after having been given antimanic drugs, the triad of hyperactivity, flight of ideas, and pressure of speech is not as obvious as their delusional thinking.

The term "paranoid" is often used incorrectly to refer to suspiciousness or persecutory beliefs. Paranoid actually means "delusional" and should be restricted as a generic term for disorders characterized by prominent delusional formation (e.g., paranoid schizophrenia and paranoid states). Paranoid schizophrenia is a schizophrenic subtype in which delusions—not always persecutory in nature—occur in abundance. In paranoid states, usually one delusional theme predominates, with no evidence of schizophrenic formal thought disorder. For example, in conjugal paranoia, a man believes that his wife is having an affair and interprets all her behavior along those lines.

Delusions can be graded on the basis of their plausibility. For instance, the false belief that one's spouse is unfaithful is nevertheless a believable idea. The false belief that one's spouse is having multiple affairs simultaneously, although delusional, is not impossible. However, the belief that one's spouse is having an affair with a creature with green tentacles is patently absurd; such bizarre delusions are the hallmark of schizophrenia, although they also can sometimes be associated with organic mental disorders.

1.7. Summary: Further Reading

The mental status examination represents the portion of the psychiatric interview that is devoted to a systematic elicitation of psychopathologic signs and symptoms that are important in diagnostic formulation. Consequently, it is essential that descriptive terms be used precisely and consistently. This will not only facilitate professional communication, but will also enhance the chances of formulating differential diagnosis in a cogent way, setting the stage for rational therapy.

Further in depth classic psychopathologic evaluation can be found in the work of Frank Fish (6) and German Berrios (41). More relevant to the American scene are Morrison's *DSM-IV Made Easy* (42), Shea's *Psychiatric Interviewing* (43), and the related monograph by MacKinnon and colleagues (44). Informative writing on various rating scales can be found in Sajatovic and Ramirez (45).

Psychologists use various tests of intelligence, personality, and cognitive function. They can be useful in specific situation such as mental retardation, personality (Axis-II) and organic mental disorders. Their discussion is beyond the scope of this chapter. Two recent monographs, the Cummings-Mega *Neuropsychiatry* (46) and the Moore-Jefferson *Medical Psychiatry* (47) provide succinct coverage in relation to organicity.

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2
Syndromes of Brain Dysfunction Presenting with Cognitive Impairment or Behavioral Disturbance: Delirium, Dementia, and Mental Disorders Due to Another Medical Condition

Susan Czapiewski, M.D., M.S. and Victoria Brown-Nyseth, M.D.

Abstract Delirium, dementia and psychiatric syndromes due to medical illness exemplify how brain function influences cognition, emotion, and behavior. For each diagnostic category, this chapter addresses disease prevalence and provides specific terminology to describe brain–behavior relationships. Included are current understandings of pathophysiology, clinical tools for recognition and assessment, and treatment modalities.

Keywords Delirium · Dementia · Cognitive impairment · Behavioral disturbance · Mental disorder

2.1. Introduction

Delirium, dementia and psychiatric syndromes arising from medical illness exist in the domain of brain-behavior relationships. Historically, an arbitrary distinction has been made between "organic" conditions, associated with known brain pathophysiology, and "functional" conditions, presumably caused by a psychiatric disorder divorced from its cerebral substrate. Illness with unexplained medical pathophysiology was considered "psychosomatic." The term was used pejoratively, as if brain-derived physical symptoms were not real. The brain was the territory of neurology; the mind and behavior belonged to psychiatry. Although the specific pathophysiology of many psychiatric disorders has yet to be described, important developments in neuroimaging have allowed us to start visualizing real time connectivity between the brain, mind, and behavior. Functional imaging technology has made the philosophical notion of a divide between body and mind obsolete. The word "functional" is currently used to describe imaging techniques such as positron emission tomography (PET) or functional magnetic resonance imaging (fMRI), but also refers to adaptive performance in social, occupational, and other important areas of life. The term "psychosomatic medicine" is now applied to a subspecialty of psychiatry that provides consultation to medical and surgical patients.

Scientific interpretations of brain–behavior relationships still vary according to the observer's perspective. The situation brings to mind the fable of the Blind Men and the Elephant where a group of blind men touch an elephant, each man describing the tusk, tail, ear, or side as though it were the whole animal, and debating their findings. Neuroscientists and practitioners of psychiatry, psychology, neurology, and pathology may all describe the same phenomena using different terms. Terminology across disciplines is not always clear or consistent. This reflects the growing body of knowledge about the brain, but can be confusing for the student. Over time, knowledge will be synthesized and common cross-disciplinary descriptions of brain-behavior states will be adopted. All the while, we are increasing our understanding of how brain dysfunction due to infection,

S. Czapiewski, M.D., M.S. (✉)
Assistant Professor, Department of Psychiatry, University of Minnesota School of Medicine,
Minneapolis Veterans Affairs Medical Center, Minneapolis, MN, USA
e-mail: czapi001@umn.edu

V. Brown-Nyseth, M.D.
Department of Psychiatry, Veteran's Administration Health Care System, University of Minnesota,
CBOC NW Metro, 7545 Veterans Drive, Ramsey, MN 55303, USA
e-mail: victoria.brown-nyseth@va.gov

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trauma, tumor or a neurodegenerative process causes emotional and behavioral symptoms that are traditionally associated with psychiatric disorders such as schizophrenia and affective illness.

The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) Neurocognitive Disorders Workgroup has placed delirium and dementia under a new category, *neurocognitive disorders (NCD)*, major and minor (1). The term *delirium* has been maintained from previous manuals and is under the category of *Minor NCD*, along with signs of cognitive decline that are more severe than normal forgetfulness of aging, but do not rise to the level of dementia. Dementia is now considered a *major NCD* with a specific etiology, for example: NCD due to Alzheimer's disease or frontotemporal NCD. The DSM-5 authors take care to say that the term *dementia* is customarily applied to disorders like the degenerative dementias that are usually associated with aging. However, *neurocognitive disorder* is the preferred term for conditions affecting younger individuals such as impairment due to traumatic brain injury or Human Immunodeficiency Virus (HIV) infection.

The DSM-5 authors acknowledge that dementia is the term used more generally by many physicians and patients. This chapter will use the term dementia except in the discussion of HIV related cognitive disorders, when language preferred by the researchers will be applied.

Although patients with delirium and dementia may share mood, psychotic or anxiety symptoms with the other psychiatric disorders, the primary disturbance is that of cognition. Cognitive deficits are present in all mental disorders, but psychosis or mood changes are predominant findings in schizophrenia or mood disorders. Cognition is the ability to think, perceive, communicate, and solve problems. Cognitive domains are attention, memory, language, visuospatial, executive function, and social cognition. Cognition cannot be separated from function. A cognitively intact person can behave and function adaptively in life. Cognitive impairment makes thinking and functioning more difficult, and independent living is threatened.

The terms delirium and dementia are attributable to Celsus, a Roman aristocrat writing in the first century A.D. It was not until the twentieth century that the two disorders, which frequently co-occurred, were consistently identified in the medical literature as separate entities (2). Both represent a change from a person's baseline cognition and function. They are acquired, not developmental disorders. Delirium and dementia can be differentiated from one another by onset (acute or insidious), course (symptom resolution or persistent), and predominant cognitive domain affected (attention or memory, language, visuospatial, executive).

The topics reviewed in this chapter—delirium, dementia, and psychiatric syndromes due to other medical conditions—can all be mistaken for primary psychiatric disease. Knowing the age-associated onset of different psychiatric disorders, and following the patient's course over time and response (or lack thereof) to treatment can help determine if the clinical picture fits with a primary mood, anxiety, or psychotic disorder or is better explained by a cognitive or secondary disorder.

2.2. Syndromes of Brain Dysfunction Presenting with Cognitive Impairment: Delirium

2.2.1. Definition

Delirium is a disturbance of attention and awareness that arises in the context of medical illness and is characterized by acute onset and fluctuating course. It has been described in the medical literature over millennia. Hippocrates (460–366 BC) was aware of the syndrome's origin in the brain and its association with medical illness. The term *delirium is* derived from the Latin *de lira*, meaning "out of the furrow" or off the track. The student with an interest in history of medicine is encouraged to read the vivid historical descriptions of the syndrome in Lipowski's classic 1990 text, *Delirium: Acute Confusional States* (2). Although delirium had been clearly described by the turn of the twentieth century, little was known about its etiology. In 1959, Engel and Romano (3) published the first study to use both descriptive and experimental research methodology, employing the electroencephalogram (EEG), to examine the pathophysiological mechanisms underlying delirium. Their publication named delirium "a syndrome of cerebral insufficiency," similar to syndromes associated with renal, cardiac, hepatic, and pulmonary insufficiency.

Despite longstanding description of delirium signs and symptoms in the medical literature, the syndrome remains underrecognized or mistaken for psychiatric illness (4) and there is significant chaos surrounding terminology. Poorly defined terms like *encephalopathy*, *confusion* or *altered mental status (AMS)* can be seen in medical records. When delirium is taken simply as a phenomenon of illness or aging, and not recognized, the consequences for patients can be dire. In the hospital, where the syndrome is common, the delirious patient is at risk for increased morbidity and mortality. Hospital length of stay is increased and there is a greater chance of being discharged to a skilled nursing facility than to home.

2.2.2. Etiology and Pathogenesis

Understanding delirium involves comprehension of the process of directing, focusing, sustaining, and shifting attention. At any given moment, the brain receives an overwhelming amount of sensory input, from its internal and external environments, and yet, when functioning properly, is able to focus on some things and ignore others in order to create a coherent perspective and

function adaptively in an ever-changing environment. Attention involves the complex cognitive processes by which salient environmental information can be selected and irrelevant information ignored (5). In delirium, selective attention is impaired. Without attention, other cognitive domains cannot be usefully employed and the central nervous system (CNS) as a whole temporarily malfunctions.

Delirium can be triggered by any event or disease process that directly or indirectly disrupts the integrity of CNS function. Although the list of potential etiologies is long, identification of a cause or causes is important to diagnosis and critical to treatment. Detecting and treating the underlying illness or condition contributes to the resolution of CNS dysfunction. The DSM-5 separates conditions responsible for delirium into cases due to substance intoxication or withdrawal; induced by medications; due to another medical condition, multiple etiologies, unspecified or unknown (1). Detective work, using the history, chart, laboratory results, imaging and medication notes, may uncover the factors involved but assigning primacy of cause may not be possible. Often, multiple factors converge to precipitate delirium.

Many medical illnesses can cause delirium. Severity of illness is a risk factor.

Terminal illness regardless of cause can be associated with delirium (6). Failure of other organ systems, such as heart, lungs, liver, and kidney is frequently associated with brain dysfunction, causing changes in cognition and perception. Hepatic encephalopathy, caused by such diverse conditions as viral hepatitis or alcoholic cirrhosis, represents a well-described type of delirium with treatment options that can reverse or minimize the impact of liver failure on brain function. Delirium is more likely to appear with acute organ failure; for example, the brain can adapt over time to chronic hypoxia from emphysema but cannot function adequately in the face of decreased oxygen saturation associated with acute pulmonary failure.

Fluid (e.g., dehydration) and electrolyte (e.g., hyponatremia) disturbances can result in delirium with resolution occurring after homeostasis is restored. Restoration of normal cognitive capacity can lag behind correction of any metabolic disturbance, so a person may appear confused despite normal laboratory values. Various infections can cause delirium, either directly (e.g., septicemia) or indirectly (e.g., hypoxia associated with pneumonia). Delirium can result from intracranial processes even in the absence of focal or lateralizing neurological signs. For example, a seizure can be followed by disorientation and perceptual difficulties. The acute phase of recovery from traumatic brain injury is frequently associated with delirium.

At times the cause of delirium can be iatrogenic, with medical treatments or prescribed medications contributing to the clinical picture. Surgical procedures are associated with an increased risk of delirium. Any patient recovering from anesthesia has a brief interval of impaired cognition. In a small proportion of post-anesthesia patients, this transient episode can be prolonged; and when it is associated with agitation, critical care in post-procedure areas can be difficult and recovery delayed. Delirium can appear hours or days after the operation as the result of overtreatment or undertreatment of pain, or complications such as infection or metabolic abnormalities.

Over the counter, herbal or prescribed medications and other substances are associated with delirium (see Table 2.1). CNS active drugs or toxins are more likely to trigger delirium than drugs that act peripherally. Other causes of delirium, such as those attributable to toxins (lead, ethylene glycol, methanol, carbon monoxide) are rare. Intoxication from drugs of abuse can be associated with delirium; and in the case of alcohol, benzodiazepines, and barbiturates, withdrawal can precipitate delirium. When alcohol withdrawal is complicated by delirium, the term "delirium tremens" is used. Delirium tremens is a serious complication that affects 5–10% of patients admitted to the hospital with alcohol withdrawal (7). Because excessive alcohol use can often be associated with other causes of delirium such as liver failure, seizures, fluid and electrolyte disturbances and trauma, a confused patient with a positive alcohol drug screen needs a thorough and thoughtful medical evaluation.

Drugs with anticholinergic properties, of which there are many, pose an increased risk of delirium. Over-the-counter medications containing diphenhydramine, for treatment of upper respiratory infections, allergies, or insomnia, are highly anticholinergic. Commonly prescribed medications with anticholinergic properties include H2 antagonists (e.g., ranitidine), and oxybutynin. Herbal preparations such as those made from jimsonweed or ma huang are associated with delirium (8).

Abnormal electroencephalographic (EEG) readings are frequently observed during delirium and are consistent with cortical dysfunction. Subcortical structures like the reticular formation and thalamus drive cortical electrical rhythms implicating the involvement of these structures in delirium. Any toxic or metabolic disturbance severe enough to cause delirium, such as acute

Table 2.1. Examples of drugs and other substances associated with delirium.

Alcohol	Benzodiazepines
Anesthetics	Botanicals (e.g., morning glory)
Antiarrhythmics	Corticosteroids
Anticholinergics	Herbal remedies (e.g., ma huang)
Anticonvulsants	Lithium
Antidepressants	Metals and related compounds (e.g., mercury)
Antihistamines	Muscle relaxants
Antihypertensives	Opioid analgesics
Antiparkinsonian agents	Organic solvents (e.g., gasoline)
Barbiturates	Organophosphate insecticides

renal or hepatic failure or drug overdose, will usually result in impaired cortical neuronal function and be evident on the EEG, manifest by diffuse slowing of the background rhythm or the superimposition of generalized slow rhythms (9).

Neurotransmitter and neuroendocrine dysfunction, and inflammation have been implicated in delirium pathogenesis. Pathways that involve the neurotransmitters acetylcholine, serotonin, dopamine and histamine appear vulnerable (10), as are those of the more widespread gamma-aminobutyric acid (GABA) and glutamate. The cholinergic theory of delirium involves a relative inhibition of central cholinergic neurotransmission. Neurohumoral theories are based on the pervasive impact that substances such as corticosteroids have on CNS function. Another theory involves the role of inflammatory responses on the brain. Inflammation can lead to the dysfunction of endothelial cells (including those making up the blood–brain barrier) during critical illnesses. As the blood–brain barrier becomes more permeable, this leads to neuronal inflammation and tissue damage (11).

Further investigations into the mechanisms underlying delirium have prompted functional MRI studies. One small study found that alterations in the reciprocity between the posterior cingulate cortex and the dorsolateral prefrontal cortex could be a partial explanation of impaired attention in delirium (12).

2.2.3. Epidemiology

The prevalence of delirium is difficult to determine, in part because the disorder is transient and generally confined to a medically ill population. Much effort has been devoted to estimating the frequency of delirium in hospitalized patients (13, 14) with insufficient attention paid to other institutional settings like nursing homes. Patients can present to the hospital already delirious or can become delirious during their stay. The prevalence of delirium in general medical-surgical inpatient populations at presentation is conservatively estimated at 10–15% and slightly higher in the elderly (15–20%). Incident cases during hospitalization are estimated to be roughly similar. Although advanced age is a risk factor, delirium can occur at any age. The disorder in children is associated with infection and medication (15). The rate of delirium is higher following medical and surgical procedures, and increases with the more invasive and extensive procedures. Intensive Care Unit patients, who are sicker, frequently experience delirium with rates as high as 80% reported (16). Vision or hearing impairment, preexisting cognitive dysfunction, and polypharmacy also add to the risk of delirium.

2.2.4. Pathology

Description of the neuropathological changes associated with delirium is complicated by the brief duration of the syndrome and comorbid factors, such as dementia. The neuropathology literature focuses mostly on forensic topics such as homicide or iatrogenic disease. There may be subtle, poorly described alterations in brain structure that reflect the deliriogenic agent. For many specific agents (carbon disulfide, organophosphates, *n*-hexane), the brain appears grossly normal. Other toxic agents (lead, ethylene glycol, methanol) may be associated with edema, in some cases (cyclosporine, tin) most prominent in the white matter. Stimulants (cocaine, amphetamines) are associated with infarcts, reflecting the cardiovascular effects of these drugs. Microscopic vascular changes may be striking, including hemorrhage (arsenic, lead) and vasculitis (amphetamines). Neuronal loss may be obvious in the case of excess mercury or lithium with preferential effects on the pallidum in the case of methanol or carbon monoxide, and the cerebellum with ethanol or phenytoin. Gliosis may point to lithium and lead toxicity and demyelination is seen in methotrexate overdose. Sometimes the findings are quite specific, as with ethylene glycol poisoning causing deposition of calcium oxalate crystals (17).

2.2.5. Clinical Picture

Disturbances of attention and awareness are central to the clinical presentation of delirium. Patients with delirium have difficulty staying alert and focused, and appear to be flooded with incoming stimuli, no longer capable of responding adaptively in a given situation. For the clinician, completing a history and examination can prove difficult with a patient who is unable to maintain meaningful engagement. The clinical interview may be brief as the delirious patient "drifts off" or appears to grasp and respond to only fragments of the dialogue. The patient may perseverate on answers to previous questions, unable to shift away from that topic. With the examination finding of an attention deficit, only the history is needed to make the diagnosis. It is useful to take the time to interview collateral sources such as family, friends, and caregivers.

Delirium typically develops over hours to days and fluctuates in severity throughout the day. When a clinician sees a calm, pleasant patient on rounds in the morning and later that day receives notification from caregivers that the patient is confused and agitated, the cause is delirium until proven otherwise. Often, nursing staff are an important source of information leading to accurate diagnosis.

Carefully reviewing risk factors that either predispose patients to developing delirium or precipitate delirium is of utmost importance (18). While reviewing medication lists it is useful to keep in mind the principle of "addition by subtraction." This principle includes the idea that reduction in dosage or removal of nonessential medications (subtraction) can elicit a positive clinical response (addition). Regularly screening hospitalized patients with risk factors for the development of delirium is recommended. Multiple bedside instruments are available for use in assessing patients for delirium, one of the more common tools is the Confusion Assessment Method (CAM) (19).

Because attention is required for any other cognitive domain to function properly, delirious patients will have a transient disturbance in memory and learning, executive function, language or visuospatial perception. More generally, thought is slowed, disorganized and fragmented. Reasoning is defective and problem-solving ability is drastically reduced.

Serial cognitive examinations over time can capture cognitive fluctuations. Unfortunately, "AOX3" (alert, oriented to person, place, time) is often the only cognitive finding documented in the medical record. This is not an adequate examination. It provides information about level of consciousness but little else that is useful. Disorientation is a non-focal finding, which can be found in other cognitive disorders, such as dementia.

Brief but effective cognitive examinations cover attention, short-term memory (recall), and executive function. The Mini-Cog (20, 21) is a well-validated screening tool that takes a brief amount of time to complete. The patient is given three words to remember, a distraction task (draw a clock with hands set at 11:10) and then asked to recall the three words. Inability to recall any of the three words and/or abnormal clock draw (clock appears abnormal and/or hands set incorrectly) suggests need for further cognitive workup.

The physical examination of a delirious patient may reveal nonspecific findings such as a fine to coarse irregular tremor, asterixis, multifocal myoclonus, and various signs of autonomic dysfunction (e.g., nausea, vomiting, flushing, blood pressure changes). Other discrete medical and neurologic signs are comparatively uncommon.

Perceptual abnormalities are the most obviously "psychiatric" aspect of delirium. The patient may experience life as a waking dream. There may be misinterpretations, illusions, and/or hallucinations. Mistaking the unfamiliar for the familiar is a form of misinterpretation. During the examination or as care is delivered, strangers are likely to be misidentified as family members and the hospital room as home. Misperceptions that convert the unknown to the familiar seem adaptive. Less comforting are the propensities to perceive objects as too big, too small, moving or flowing together. Patients are also inclined to mistake common objects: spots for insects, folds in the bedcovers for snakes, or a bedpost for a rifle. Although these illusions are typically visual, they can involve any sensory modality.

Hallucinations, false sensory perceptions, are another disorder of thought content. They are nonspecific findings, requiring further investigation as to their cause. Auditory hallucinations are more likely associated with primary psychiatric disorders such as schizophrenia or depression. Presence of visual hallucinations suggests delirium. Visual perceptual abnormalities can also appear in dementia with Lewy Bodies (DLB), where patients "see" small children or animals. Auditory and tactile hallucinations can occur in delirium, but are less common.

Delusions, false fixed beliefs, are also nonspecific findings in psychiatric and cognitive disorders. Delusions in delirium are transient and, unlike those found in primary psychotic disorders, not very complex. They commonly involve persecution or vague plots against the patient. In dementia, delusions are related to the memory deficit: a wallet is lost, so it must have been stolen, or a spouse is no longer recognized, so he/she must be an imposter. Psychotic symptoms are often troubling to delirious patients and can complicate the delivery of care.

Associated features of delirium can include disturbances in the sleep-wake cycle, psychomotor disturbances and emotional disruption; these are incorporated into the International Classification of Diseases definition (ICD-10) (22). Disturbances in the sleep-wake cycle are common. The delirious patient may nap or sleep during daytime hours and be awake "all night long."

Mood and behavior are frequently disturbed. Patients with delirium can exhibit anxiety, fear, depression, irritability, anger, euphoria, and apathy. Unpredictable shifts in emotions can occur and be accompanied by behaviors such as moaning, screaming, or cursing.

Three motor subtypes of delirium have been recognized (23). A patient with the hyperactive subtype has psychomotor agitation and affective lability; that can cause behavioral dysregulation and lead to an identifiable disturbance on the medical unit. Patients with the hypoactive subtype are quiet, psychomotor retarded, sluggish, and lethargic. Their behavior is rarely a problem on the unit, but prevents them from actively participating in physical or other therapies. The third subtype, mixed, includes patients with impaired attention and awareness with either normal or rapidly fluctuating level of activity.

2.2.6. Clinical Course

Delirium is a transient illness, with acute onset and fluctuating course. Prodromal features can be present, such as vague feelings of uneasiness, irritability, and hypersensitivity to light and sounds. If a hospitalized patient appears short-tempered and belligerent, this may be a personality change brought on by incipient delirium. In general, the onset of delirium tends to be

within minutes to hours and resolves rapidly. Uncomplicated delirium in otherwise healthy patients tends to be short-lived, on the order of a week. Recovery is usually complete unless the underlying disorder cannot be redressed.

Although in the majority of patients cognitive deficits resolve completely within a week, recent investigations have shown that, in vulnerable populations, delirium can be associated with a significantly prolonged cognitive impairment on the order of months to years. One study, examining patients aged 60 years and older after cardiac surgery, revealed that patients who developed postoperative delirium were significantly less likely to have returned to their preoperative level of performance at 6 months than were patients without delirium (24). In an analysis of prospectively collected data on patients with Alzheimer's disease, the development of delirium (affecting 56% of the sample studied) was associated with an increased rate of cognitive decline that was maintained for up to 5 years (25).

Delirium is marked by wide clinical variability, even in the same patient. The severity of symptoms varies over the course of a day, and is greatest over late evening to night, when external orienting stimuli decrease. Lucid intervals are most likely to be observed in the morning. After resolution, the experience of delirium may leave the patient and family puzzled and anxious. Patients are often able to recall only bits and pieces of their experience upon recovery. Families can fear that the patient is developing schizophrenia and benefit from counseling about delirium.

Delirium superimposed on dementia may result in worsening of cognition that does not completely reverse. Delirium increases the risk of institutionalization and death in the months after hospital discharge. When delirium complicates terminal illness, it makes the final days more difficult for the patient and loved ones.

2.2.7. Laboratory Finding

Specific laboratory studies should be ordered based on evidence obtained from the history and physical examination that would suggest a causative drug or physical illness. Since causes can be multiple and the patient's physical examination unrevealing, systematic consideration should be given to studies such as electrolytes, urine drug screen, hepatic and renal function studies, TSH, vitamin B12, folate, drug levels, oxygen saturation, urinalysis, and an electrocardiogram. Central nervous system imaging is usually suggested by focal or lateralizing neurological findings and confirms the location of a lesion or lesions, for example, after a stroke. Sometimes an EEG is helpful. A diffusely slow tracing can suggest the diagnosis although slowing can be observed in other circumstances (e.g., after a seizure). A normal or fast record does not exclude delirium (9). Absence of a diagnosis after a systematic evaluation (including the tests noted above) may warrant head CT or MRI and examination of the cerebrospinal fluid although the yield from these efforts is likely to be low.

2.2.8. Differential Diagnosis

The differential diagnosis for delirium involves other disorders of cognition, primarily dementia. This distinction should center on the acute onset and disordered attention and arousal that characterize delirium; by contrast, both delirium and dementia are associated with memory impairment and perceptual disturbances (26). Fluctuating course is less helpful because patients with delirium and dementia can both experience worsening at night ("sundowning"). In circumstances where the onset of dementia can be defined (after traumatic brain injury, stroke, or resection of a brain tumor), delirium may precede the chronic deficits associated with dementia.

In many cases, delirium is superimposed on dementia. The tip-off can be an acute change in behavior, which is usually associated with illness in a demented person. In other instances, dementia can have prominent features consistent with a persistent and long-lasting delirium. This is most frequently seen with dementia with Lewy Bodies (DLB), although the persistent parkinsonian features and autonomic instability of DLB should aid in the differential diagnosis. In the absence of a good history or convincing examination, the provisional diagnosis should be delirium.

Patients with delirium can have comorbid psychiatric illnesses. While most often disorders such as depression, mania, and schizophrenia can be readily distinguished from delirium, there are a significant number of cases in which symptoms overlap. Attention deficits and fluctuating course can be helpful in separating delirium from schizophrenia and affective disorders. Hypoactive delirium can be mistaken for depression. Catatonia can be difficult to distinguish from hypoactive delirium, especially when the patient is not verbally responsive (27).

Mania and acute psychosis can be confused with the hyperactive form of delirium. Additionally, there are clinical presentations that combine features of delirium, mania, and catatonia. Unfortunately, these cases can be difficult to study partly because, as of yet, no clear consensus criteria have been defined. Names given to these presentations include delirious mania, manic excitement, Bell's mania, lethal catatonia, and malignant catatonia. Delirious mania has been described as a syndrome characterized by the rapid onset of delirium, mania, psychosis, and catatonic features (28, 29). There have been studies that suggest up to 15–20% of acutely manic patients also meet criteria for delirium. Recognition of delirious mania is very important as it can progress rapidly and become life threatening.

2.2.9. Treatment

Prevention is the ideal approach to treatment. Some research has shown that up to 40% of cases of delirium are preventable (30). One well-known delirium prevention protocol, the Hospital Elder Life Program (HELP), was developed by Dr. Sharon K. Inouye and colleagues at the Yale University School of Medicine. This protocol targets six risk factors: cognitive impairment, sleep deprivation, immobility, visual impairment, hearing impairment, and dehydration. Since 1999 hundreds of hospitals have implemented the HELP protocol, both in academic settings and community hospitals. The delivery of this protocol by special multidisciplinary teams has yielded reductions in rates of delirium and the complications of delirium in a controlled clinical trial (30). In 2010, a multidisciplinary National Institute of Health panel developed a guideline for prevention of delirium comprised of 13 clinical recommendations (31). These recommendations included assessing persons at risk for clinical factors contributing to delirium within 24 hours of hospitalization, assessing and addressing pain, and reviewing all medications. Drugs should be minimized in number and dosage. While these interventions are consistent with exemplary medical care, limitations in resources and difficulty in systematically identifying patients at risk for delirium are barriers to more widespread implementation.

In a given patient, systematic attempts should always be made to treat the cause or causes of delirium. Sometimes this effort involves the physician primarily responsible for patient care working with the psychiatric consultant. This is helpful especially when the symptoms persist despite the lack of physical or laboratory findings or when assistance with behavior management is required. Nevertheless, a systematic approach to diagnosis and treatment can lead to detection of unusual circumstances such as attempted suicide or homicide by poisoning. When delirium is a feature of terminal illness, the underlying condition is obviously not reversible.

Attention to the patient's environment can be critical to effective care. Availability of a constant attendant ("sitter") allows timely monitoring of behavior, frequent reorientation and assurance. The room should be simply and practically arranged to provide consistent environmental cueing and reassurance without excessive stimulation. Restraints are undesirable but can be necessary to prevent the patient from harming self or others and for sustaining essential treatment (32). When restraints are necessary, patients benefit from sedation, since a delirious person, inexplicably unable to move freely, is likely to become frightened and agitated.

Medications for delirium should be considered if non-pharmacological measures have been ineffective or there is considerable distress or risk of danger to self and/or others. Administration of high-potency antipsychotics such as haloperidol at low doses has been considered first line treatment in many protocols. Haloperidol is favorable because it has fewer active metabolites, limited anticholinergic effects and can be given by mouth or by intramuscular injection (IM) (33). The drug is also administered intravenously (IV), particularly in intensive care unit settings, although this is not a Food and Drug Administration (FDA) approved route of administration. Dosing is usually repeated with the frequency of administration dictated by clinical need (e.g., severity of agitation) until the reason for treatment is no longer a crisis, continued at lower doses until the delirium appears to be resolving then tapered to discontinuation.

The elderly typically require more modest doses (usual haloperidol doses, 5–10 mg; in the elderly, 1–2 mg). Haloperidol is associated with dystonic reactions (the involuntary and usually repeated contraction of a muscle or group of muscles), akathisia (restlessness), parkinsonian rigidity, and rarely, cardiac dysrhythmias such as *torsades de pointes*. Newer antipsychotics such as olanzapine and risperidone are of interest because they may have a lower risk of side effects when used for other conditions, but the data supporting the use of these compounds in delirium is not as robust as is the case for haloperidol. There have been few studies looking at the utility of antipsychotic medications in preventing the onset of delirium; one analysis suggested they might reduce the overall risk of postoperative delirium (34).

While antipsychotic medications continue to be a mainstay of treatment, two recent reviews raise questions about the use of these medications in certain populations. The American College of Critical Care Medicine assembled a multidisciplinary task force to review the literature and publish guidelines regarding the management of pain, agitation, and delirium in adults in the intensive care unit (35). This task force concluded there was no published evidence that treatment with haloperidol reduces the duration of delirium in adult patients in the intensive care unit, though there is some evidence for atypical antipsychotics. Another systematic literature review determined that due to severe methodological limitations in the studies included, the use of antipsychotics in the treatment of older hospitalized adults was not supported (36).

Other medications are of uncertain value. The cholinergic theory of delirium pathogenesis suggests that inhibition of cholinesterase, the enzyme responsible for degrading acetylcholine, could have a positive effect. Blinded, randomized clinical trials of the cholinesterase inhibitor donepezil showed little benefit in reducing the risk of postoperative delirium for elderly patients undergoing an elective orthopedic procedure (37, 38). Dexmedetomidine, an alpha$_2$ adrenergic agonist, has shown some promise as a sedating agent in the intensive care unit when compared to alternatives such as the anesthetic propofol or benzodiazepines (39). Further work is necessary to support preliminary observations. Although sedation is undesirable, sometimes use of propofol or a benzodiazepine (e.g., lorazepam) is necessary because haloperidol and related compounds are not sufficient for symptom control.

Complicated alcohol withdrawal, delirium tremens, is one of the most common causes of delirium in hospital settings. Treatment is best accomplished with benzodiazepines such as lorazepam, diazepam, midazolam, and chlordiazepoxide (7). While all of these benzodiazepines can be given orally and intravenously, lorazepam may be the drug of choice because it can also be administered intramuscularly. Lorazepam may also be favorable in some situations, such as in patients with decreased liver function, because it does not have active metabolites. Delirium precipitated by benzodiazepine withdrawal can also be treated with benzodiazepines, with a plan for a gradual taper. Phenobarbital, a barbiturate, is rarely used but may have a role in the treatment of delirium associated with barbiturate withdrawal, benzodiazepine withdrawal or in neonatal abstinence syndrome (40). Finally, haloperidol and other antipsychotics may be used as an adjunct in some patients with delirium tremens, benzodiazepine withdrawal delirium or barbiturate withdrawal delirium because benzodiazepines may provide insufficient symptom control, especially in the case of multifactorial delirium.

2.3. Dementia

2.3.1. Definition

Dementia is a syndrome of acquired, persistent cognitive and behavioral deficits that interfere with the ability to function socially or at work or to perform usual activities (41). The term "dementia" comes from the Latin *dement,* meaning "to be out of one's mind."

Aractaeus, in the second century, associated the global dysfunction characteristic of dementia with aging. Although aging is the greatest risk factor for dementia, disease is not the inevitable result of growing old. Dementia symptoms represent a change from baseline. The person with dementia experiences difficulties with cognition and function that are a departure from a lifetime of thinking, perception, communication, and problem solving. The presence of cognitive impairment transforms emotional experience, personality and behavior. An extrovert can become socially withdrawn and isolative or a formerly thoughtful and conscientious person can show disregard for the feelings of others and engage in antisocial behavior. Performance in work or daily tasks is impaired. A surgeon with early dementia may forget operating room procedure and make an error that puts a patient at risk. A formerly reliable driver may get lost in a familiar place, panic and cause a motor vehicle accident. As these examples show, cognitive and functional decline affects not only the person but also a wider circle of family, friends, colleagues, and society.

Dementia is a clinical diagnosis, based on specific criteria. In the clinic, symptoms of dementia are elicited by a combination of history taking and an objective cognitive assessment. Since the cognitively impaired person may not be aware of any problems, it is essential to obtain corroborative history from a knowledgeable informant. Cognition can readily be assessed through a focused mental status examination (see Sect. 2.3.5). Cognitive domains are attention, memory (the ability to learn and remember), language (receptive and expressive speaking, reading or writing), visuospatial abilities (recognizing faces or objects; the ability to navigate while driving or walking), executive function (planning, organizing, decision making, monitoring, mental flexibility, the ability to use environmental feedback to guide behavior), and personality and behavior (social cognition). According to the NIAA-AAA criteria (41), diagnosing dementia from any cause requires deficits in two or more cognitive domains (see Table 2.2). Symptoms cannot be explained by delirium or a major psychiatric disorder.

There are many causes of dementia. Etiologies can include neurodegeneration (Alzheimer's disease, frontotemporal dementia, Lewy Body disease), stroke, infections (HIV, Creutzfeld Jacob), central nervous system neoplasms, traumatic brain injury, toxins (e.g., alcohol), autosomal dominant mutations (Huntington's Disease), and iatrogenic (radiation or surgery induced). The course of most dementias is progressive. Head injury and vascular disease (a stroke risk factor), which cause static cognitive impairment, increase the likelihood of developing a degenerative dementia as well (42).

TABLE 2.2. Core clinical criteria for dementia, any cause.

Cognitive or behavioral symptoms that interfere with ability to function at work or usual activities and represent a decline from previous levels of functioning and performing
Symptoms are not explained by delirium or major psychiatric disorder
Impairment is detected and diagnosed through history and objective cognitive assessment
Impairment involves a minimum of two of the following:
• Learning and memory
• Executive function
• Visuospatial abilities
• Language
• Changes in personality, behavior, or comportment

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Over several decades, expert work groups have developed and revised diagnostic criteria for the different dementias according to research findings. In earlier consensus criteria (43), systemic disorders such as thyroid disease or vitamin B12 deficiency were thought to commonly mimic Alzheimer's disease (AD) and should be ruled out prior to the diagnosis being made. This notion of "reversible dementia" is no longer widely held. Clinical and research experience have shown that in the presence of signs and symptoms of AD, thyroid or B12 replacement does not alter the progressive course of the dementia (44).

Dementia syndromes can be subdivided into those involving the cerebral cortex and subcortical brain systems. In the brain, these systems are interconnected and overlapping but the concept of cortical and subcortical dementia may shed light on the mechanisms underlying both cognitive and psychiatric disorders. Previous DSM iterations used only cortical symptoms to define dementia: memory impairment, aphasia, apraxia, and agnosia. Anatomically, these symptoms are localized to the temporal and parietal lobes of the brain. Alzheimer's disease (AD) is the prototypic cortical dementia. Subcortical brain systems are involved in the regulation of a variety of cognitive and emotional processes. Pertinent subcortical regions include the basal ganglia, thalamus, and white matter connections to the frontal lobes (45). Impairments that occur in these systems are often confused with primary psychiatric disorders. Subcortical cognitive impairment can present with emotional dysregulation, apathy, slowed cognitive processing and executive dysfunction. This can look like depression, without the sadness and emotional distress. Subcortical system lesions can occur with frontal axonal shear-strain in traumatic brain injury, lacunar infarcts in the basal ganglia, Parkinson's disease and HIV neurocognitive impairment. With subcortical cognitive dysfunction, cortical domains such as memory, language, and visuospatial function are better preserved (46). There is significant clinical symptom overlap between lesions in the frontal-subcortical circuits underlying motivation, executive function, and personality and cortical lesions involving the frontal lobes. These will be described in more detail in the discussion of frontotemporal dementia.

In short, there are many ways to approach the topic of dementia. This chapter will focus on three broad categories of dementing illness: dementias that are commonly seen in clinical practice and have a strong research base (Alzheimer's, dementia with Lewy Bodies), one that is often mistaken for a primary psychiatric disorder (behavioral variant of frontotemporal dementia) and a subcortical dementia that has influenced the psychiatric nosology in DSM-5 (major neurocognitive disorder due to HIV).

Alzheimer's disease is the most common dementing illness. This fatal neurodegenerative disease was initially described by the psychiatrist Alois Alzheimer (1864–1915) who described "a peculiar disease of the cerebral cortex" (47) involving a 51-year-old woman, Auguste Deter, who was institutionalized and died with impaired memory and language, psychosis, and global functional deficits. Alzheimer's description was facilitated by a new technology. His colleague, the pathologist Franz

TABLE 2.3. Diagnostic criteria for probable Alzheimer's disease dementia.

Meets criteria for dementia (see Table 2.2)
Insidious onset over months–years
Clear cut history of worsening of cognition by report or observation
Initial and most prominent cognitive deficits are evident on history and examination in one of the following:
- Amnestic presentation: impairment in learning and memory (most common)
- Non amnestic presentations: language, visuospatial, executive

Exclusionary criteria: recent stroke temporally related to onset or worsening of cognitive impairment; core features of dementia with Lewy bodies; prominent features of a frontotemporal dementia variant; or evidence of another medical, neurological, or medication-related reason for cognitive decline

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TABLE 2.4. Cognitive domains, symptoms/observations, and history/examination findings.

Cognitive domain	Symptoms or observations	History/examination findings
Attention	Inability to focus, direct, sustain, and/or shift attention appropriately	Dozing, somnolent, cannot keep eyes on examiner or follow directions, distractable
Memory	Inability to learn and remember	Cannot give accurate historical information, poor recall on Mini-Cog
Language	Trouble with expressive and receptive speaking, reading, writing	Word finding difficulties, paraphasic errors, empty speech
Visuospatial/ perceptual-motor	Inability to recognize faces, objects or navigate in space (driving, walking), apraxia (tools, sewing)	Family has concerns about driving or tool use, wandering, abnormal clock draw on Mini-Cog
Executive function	Inability to plan, organize, make decisions, self-monitor or use environmental feedback to guide behavior; lack of mental flexibility	Cannot effectively manage finances, chronic illness, medications or appointments; trouble shopping or cooking; abnormal clock draw on mini-cog
Personality and behavior, social cognition	Poor social skills; speech or behavior outside socially acceptable norms; inability to read social cues or facial expressions	Personality change, lack of empathy, poor social skills, antisocial behavior; dressed or acts inappropriately, perseverative, impersistent

Nissl had recently developed a method for staining nerve tissue. This technique allowed Alzheimer, at autopsy, to visualize for the first time neurofibrillary tangles that, along with amyloid plaques, are pathognomonic for the disease that would bear his name. This was the first of many technological innovations over the years that have allowed us to connect brain and behavior.

Currently, the diagnosis of AD is made when the patient meets criteria for dementia (see Tables 2.3 and 2.4), with insidious onset and gradually progressive course. Cognitive impairment is most commonly related to memory, plus deficits in executive, visuospatial and/or language function; and/or personality change. Strong historical, clinical, and/or neuroimaging evidence of another dementia precludes the AD diagnosis. There are uncommon variants of AD that present with primary visual or frontal deficits (41).

Dementia with Lewy Bodies (DLB) falls under the broader category of Lewy Body diseases. Persons with DLB have dementia plus the neuropsychiatric, motor, sleep, and autonomic symptoms that are associated with the other Lewy Body diseases: Parkinson's disease and Multiple System Atrophy. They exhibit the parkinsonian tremor, bradykinesia, and gait disturbance as well as repeated falls, syncope, and autonomic dysfunction. Attention and alertness fluctuate throughout the day. Complex, recurrent visual hallucinations can occur, usually of small children or animals. Treatment of the hallucinations is complicated by the fact that patients are very sensitive to antipsychotic side effects (48). REM sleep behavior disorder (RBD) often presents decades before the neurodegenerative disease becomes clinically evident (49). Persons with RBD, usually elderly males, have vivid, often frightening dreams. The accompanying loss of REM atonia results in dream enactment behavior, which can cause injury to the patient and bed partner.

Vascular dementia is defined as dementia that occurs within three months of a cerebrovascular event, is accompanied by focal findings on neurological examination and exhibits cerebral lesions on neuroimaging that correlate with the identified cognitive deficits. Lesions can be the result of ischemic, hemorrhagic, and hypoxic (cardiac arrest, pulmonary failure, CO poisoning) events (50).

Frontotemporal disorders causing dementia can best be understood in the context of the frontal lobes of the brain, which are composed of the prefrontal and motor cortices. Extensive white matter tracts conduct the reciprocal interactions between the frontal cortex and subcortical regions such as the thalamus and limbic system. Unlike more posterior brain regions, the frontal lobes have more white matter and less collateral vascular circulation, leaving them susceptible to traumatic injury, chronic hypoxia, and watershed infarcts. White matter tracts connecting the frontal lobes and subcortical regions form part of the striatum, which is susceptible to hypertensive (lacunar) infarcts (51). A subcortical, striatal lesion in a strategic location can create the same clinical picture as frontal cortical damage.

The neuroanatomic proximity between the prefrontal cortex and the motor strip and extensive reciprocal circuits connecting the frontal lobe to the limbic system predict the complex interaction between emotion, thought, and behavior. Functionally, the frontal lobes take information from throughout the brain, integrate environmental and emotional information, formulate an action plan, initiate motor activity, and ultimately mediate action on the environment (52).

Intact frontal cortical function is crucial to effective social interactions. Frontal lobe damage causes significant changes in personality and behavior. The most famous example of this is the case of Phineas Gage who, in 1848, sustained a traumatic frontal lobe injury in a railroad construction accident. Twenty years later his treating physician, Dr. John Martyn Harlow, described his former patient as:

> *Fitful, irreverent, indulging at times in the grossest profanity (which was not previously his custom) manifesting but little deference for his fellows, impatient of restraint or advice when it conflicts with his desires, at times pertinaciously obstinate, yet capricious and vacillating, devising many plans of future operations, which are no sooner arranged than they are abandoned in turn for others appearing more feasible. A child in his intellectual capacity and manifestations, he has the animal passions of a strong man…his friends and acquaintances said he was "no longer Gage"* (53). Gage's disinhibition, indifference to others, willfulness, executive dysfunction, inflexibility, perseveration and impersistence at a task are examples of frontal dysfunction.

Frontotemporal dementia (FTD) is a degenerative dementia with three clinical variants: behavioral, language and motor. The behavioral variant (bvFTD) is the most common form and the most likely to be mistaken for psychiatric illness. Persons with bvFTD can act like Phineas Gage, although the behavior begins insidiously. The bvFTD patient will show early symptoms of socially inappropriate behavior, apathy or inertia, loss of sympathy or empathy, stereotyped and perseverative behaviors, hyperorality, and/or dietary changes. Episodic memory and visuospatial skills are well preserved early in the course of the disease. Diagnosis is made by observation or history provided by a knowledgeable informant (54).

Many persons with bvFTD are initially misdiagnosed with psychiatric illness. Apathy can be mistaken as depression. Disinhibition and impulsivity mimic anxiety, bipolar or a personality disorder (55). However, psychiatric hospitalization and treatments are either ineffective or cause worsening of cognitive and motor symptoms (56). Social consequences of bvFTD can be extreme. Acquired sociopathic behavior such as shoplifting, driving violations, inappropriate sexual behavior, and violence can result in incarceration (57).

HIV-associated neurocognitive disorders (HAND) have been classified into three subtypes ranging in severity from asymptomatic to dementia, for which the preferred term is major neurocognitive disorder due to HIV infection (MND-HIV). MND-HIV causes predominantly subcortical dysfunction. Patients show difficulty with sustained attention and concentration, slowed psychomotor processing speed, and executive dysfunction (46).

2.3.2. Etiology and Pathogenesis

Despite the tremendous amount of research on the dementias over the past decade, the complexity of brain function has complicated our understanding of etiology and pathogenesis. Progress, however, has been made in developing better diagnostic criteria and in elucidating genetic and molecular biological determinants of the disease.

Dementia disconnects the complex physical, electrophysiological and neurochemical systems that allow humans to function adaptively in the world. Dementing illness involves selective loss of cortical neurons, disruption of white matter tracts, synaptic degradation, neurotransmitter deficits and desynchronization of neural network activity. This occurs via multiple mechanisms: trauma, cerebral infarction, infection, tumor, post-radiation, or neurodegenerative disease. The majority of dementias are neurodegenerative. Proposed mechanisms of neurodegeneration include toxic protein accumulation, pro-inflammatory responses, mitochondrial dysfunction, oxidative stress, genetic and environmental factors, and apoptosis (42).

Especially in Alzheimer's disease (AD), the lines of demarcation between illness and normal cognitive changes in aging are not clear. Normal cognitive aging involves slowed information processing, impaired vigilance, and inefficient executive function. New memories can be stored long term, although access to those memories may take time and effort (58). Deficits are rarely evident outside of a formal neuropsychological evaluation. However, despite relatively intact cognition and function, brains of non-demented elders may show pathological changes associated with dementia (59).

AD is a multifactorial disorder. A complex association between environmental or lifestyle and polygenetic factors likely plays a crucial role in vulnerability (42). Mediators of AD vulnerability and protection include cerebrovascular disease, genetics, TBI, toxins such as alcohol, smoking, and diabetes. Midlife vascular and metabolic disorders are important risk factors for AD. Hypertension, hypercholesterolemia, cardiovascular disease, and carotid artery stenosis increase the risk of dementia. In genetically susceptible hosts, atherosclerotic lesions and other vascular changes lead to chronic cerebral hypoperfusion and may converge to initiate or accelerate the neurodegenerative processes in an aging brain. Combined cerebrovascular disease and Alzheimer's pathology predicts a more rapid decline in cognition and function (60). Diabetes and impaired glucose tolerance may play a role in dementia pathogenesis. The exact mechanism is unclear but there may be a direct effect of glucose-mediated toxicity and hyperinsulinemia on amyloid metabolism and neurodegeneration (42).

Protective factors for neurodegenerative disease include physical and cognitive activity and maintaining social connections. There is a growing literature showing the neuroprotective benefits of aerobic exercise, especially in middle age. Exercise may even attenuate cognitive decline in persons diagnosed with dementia (61). Light to moderate alcohol consumption, especially wine, may protect against dementia (62).

Although the majority of AD cases are sporadic, there are rare genetic familial forms, which are thought to be autosomal recessive (63). Three genes have been implicated: amyloid precursor protein (APP), presenilin 1 (PSEN1), and presenilin 2 (PSEN2). Persons with Down Syndrome (Trisomy 21), with three APP copies, are very likely to develop AD (42).

Late onset AD, occurring >60 years of age, is a polygenic disease that accounts for nearly 95% of all cases. Although the major risk factor is age, genetic factors like the apoliproprotein E ε4 (APOE4) further increase the chance of developing AD and reduce the average age of disease onset (42).

The acknowledged hallmark of AD is the deposition in brain parenchyma of two abnormal proteins: Aβ as amyloid plaques and tau as neurofibrillary tangles. Amyloid plaque burden is not associated with dementia severity, but greater neurofibrillary tangle density correlates with cognitive dysfunction (42). Accumulation of tau in neurofibrillary tangles is not specific to Alzheimer's disease and has been associated with other dementing illnesses, including FTD.

The sequence of events involved in AD pathophysiology continues to be vigorously debated in the scientific literature. Evidence suggests that the neurodegenerative process of AD begins years, if not decades, before the clinical diagnosis of dementia (64). Synaptic loss in the hippocampus and other cortical regions is widely considered the major pathophysiological correlate of cognitive decline. Defects in synaptic transmission occur early in the disease and progress slowly (42). Deficits in acetylcholine, a neurotransmitter involved with memory, and toxicity from the excitatory neurotransmitter glutamate are involved in the pathogenic process and are the targets of current medications to treat AD.

The amyloid β protein (also known as Aβ) derives from a sequential cleavage of the amyloid precursor protein (APP). It can vary in length, according to the pattern of cleavage of APP. The Aβ1-42 (also known as Aβ42) isoform has hydrophobic properties and aggregates more readily than the Aβ1-40 form, contributing to plaque formation.

In the normally functioning neuron, the protein tau is responsible for the assembly and stability of microtubules, and axoplasmic transport (transporting proteins, neurotransmitters, hormones, and enzymes along the axon toward the cell body or toward an axon terminal). Abnormal phosphorylation of tau causes it to detach from axonal microtubules and aggregate into insoluble neurofibrillary tangles. Subsequent neurofibrillar degeneration may trigger or facilitate multiple pathological changes that affect mitochondrial dysfunction and neuronal damage (42).

The pathogenic sequence of interactions between Aβ and tau proteins has been extensively investigated and still remains a subject of scientific debate. In the rare early onset familial forms of AD, the "amyloid cascade hypothesis" appears to be valid. Excessive formation and deposition of Aβ, with consequent aggregation in plaques, initiates a neurotoxic cascade (including

neurofibrillary tangle formation) and ultimately leads to synaptic and neuronal loss. In the more common age-associated form, the pathogenic trigger remains unidentified (42).

There is a great deal of research interest in the symptomatic pre-dementia stages of Alzheimer's disease, when the characteristic pathological changes, but not dementia, are present. AD begins insidiously, with no fixed events that define its onset. In an attempt to identify transition points, the concept of Mild Cognitive Impairment (MCI) has been developed (65). MCI is a syndrome defined by clinical, cognitive, and functional criteria. Amnestic and non-amnestic subtypes have been described. Amnestic MCI appears most likely to convert to AD over time. Persons with amnestic MCI have memory complaints and preserved independence in functional abilities. However, they show mild difficulty with complex functional tasks they had habitually performed, such as paying bills, preparing a meal, or shopping. They may take more time, be less efficient, and make more errors at performing such activities than in the past. Nevertheless, they generally maintain their independence of function in daily life, with minimal assistance. These patients should be followed longitudinally: cognition and function monitored over time (66). Trials of acetylcholinesterase inhibitor drugs in MCI have not shown any effect in slowing conversion to dementia (65).

Dementia with Lewy Bodies (DLB) is characterized by Alzheimer's pathology and Lewy Bodies, which are pathological cytoplasmic accumulation of α-synuclein. Other synucleinopathies such as Parkinson's disease and Multiple System Atrophy share many clinical features with DLB and can progress to dementia. The presence and onset of visual hallucinations in DLB is associated with loss of neurons in the anterior and inferior temporal lobe and amygdala. These areas of the brain are implicated with generation of complex visual images (48).

Vascular dementia has an abrupt onset and is classically described as having a stepwise course. A single stroke can readily be associated with a specific cognitive deficit, such as a left middle cerebral artery thromboembolism resulting in aphasia; but the broad range of findings that constitute dementia is typically the result of multiple vascular events. The loss of blood supply results in neuronal death; current hypotheses about CNS vascular lesions suggest that other factors, including glutamate toxicity and calcium imbalance, are toxic to neurons.

Neuropathological and imaging studies of early bvFTD suggest that the disease begins in the nondominant anterior cingulate cortex (ACC) and frontoinsula (FI), then spreads to a circumscribed network of anterior brain regions. The ACC and FI contain von Economo neurons, which may be involved with creation of internal representations of the autonomic nervous system (67). One model of ACC and FI functioning proposes that cells in these structures, including the von Economo neurons, anchor the neural representation of emotional awareness and play a role in consciousness (68). As neurodegeneration progresses, patients with bvFTD lose emotional-moral and contextual sensitivity; the loss of which facilitates their uninhibited, socially disadvantageous behavior (67).

In contrast with AD, the cholinergic system in FTD appears to remain intact. The frontal cortex has multiple serotonergic projections from the raphe nuclei (69), and many of the behavioral manifestations of bvFTD can be moderated by serotonergic medications.

FTD has a strong genetic component. Approximately 40% of patients report a positive family history of dementia; of which one-third to one-half follow an autosomal dominant inheritance pattern. Many genes have been identified; the most common of which are: MAPT (microtubule-associated protein tau), PGRN (progranulin), and C90RF72, a recently identified hexanucleotide repeat expansion on chromosome 9. There may be a connection between the specific gene mutations and patterns of brain atrophy (69).

HIV infection can cause MND-HIV (dementia) either as a result of viral effects or because immune suppression predisposes to cancers or opportunistic infections. The exact mechanism of neurodegeneration leading to HIV-associated MND is unclear. There is no in vivo evidence that HIV directly infects neurons. The current, "indirect" model involves virus-bearing peripheral monocytes and lymphocytes. These infected cells migrate across the blood brain barrier and differentiate into macrophages that release proinflammatory cytokines/chemokines and substance P. This process ultimately impairs the neuroprotective activity of astrocytes and contributes to a neurotoxic environment involving increased permeability of the blood brain barrier, the release of excitatory amino acids (eg, the neurotransmitter glutamate), free radical production, oxidative stress, and dopamine dysregulation (70).

This summary gives a glimpse of the recent and remarkable accumulation of scientific knowledge of the dementias, particularly on the descriptive, biochemical and genetic fronts. We know that regular physical exercise, especially in middle age, is neuroprotective. Lifelong learning, managing vascular risk factors, and preventing traumatic brain injury (wearing seatbelts and bike helmets) will decrease disease risk. Nevertheless, much remains to be learned, including the process by which molecular lesions initiate the path to neuronal degeneration and death. How is it that ubiquitous proteins start aggregating within the brain and produce relatively specific syndromes? What is the sequence of events in the transitions from normal aging to "preclinical" to full blown Alzheimer's disease? How do we take advantage of the delay between illness onset and clinical symptoms to halt the neurodegenerative process? Future therapies will be based on improved understanding of dementia etiology and pathogenesis.

2.3.3. Epidemiology

Dementia prevalence rates vary among studies, depending on setting and diagnostic criteria, but it is clear that cognitive impairment and dementia are strongly associated with increasing age. However, it should be emphasized that dementia does not appear to be an inevitable consequence of growing older. Even after age 90, only 37.5% of persons have Alzheimer's disease, the most common dementia (71). Mild cognitive impairment (MCI) has been documented in more than one in ten seniors over age 70, with more than 20% affected after the age of 80 years (72). Over five years, approximately one out of five persons with MCI is likely to progress to AD (72).

AD accounts for 60–90% of all dementias. The older a person is when diagnosed with dementia, the more likely it is to be AD. The incidence of AD is approximately 1% at age 60 and roughly doubles every 5 years afterward. The estimated lifetime risk of AD is 10–11% in men and 14–17% in females. The gender difference is thought to be due to women's longer life expectancy (42).

FTD is considered the third most common dementia overall, after AD and DLB, but is the leading cause of dementia in persons <60 years old. US prevalence in persons aged 45–64 years is estimated to be between 15 and 22 cases per 100,000. Onset is usually in the 50s, but the range can be anywhere between ages 30–90. Men and women are equally affected (69).

Introduction of effective HIV treatment has had a positive impact, making MND (dementia) a less frequent finding (73). Nearly half of all HIV/AIDS patients have milder, more slowly progressing cognitive impairment (74). Of the 80% of IV drug abusers receiving psychiatric care in one methadone maintenance program, one in five was receiving treatment for a neurocognitive disorder, presumably related to HIV infection. Among patients medically hospitalized for complications of HIV/AIDS, 19% were found to have delirium or dementia (75).

2.3.4. Pathology

The diagnosis of a specific dementia is primarily made based on clinical criteria, but pathology provides insights into disease pathogenesis and plays a supporting role in diagnosis (Alzheimer's disease) or contributes to classification based on histopathology (frontotemporal dementia). In Alzheimer's disease (AD) structural changes are often evident on inspection of the brain postmortem (17). Gross findings are prominent cortical sulci and narrowing of gyri with relative preservation of the cerebellum. The atrophy associated with AD usually results in a brain that weighs substantially less than the brain of persons without dementia.

Histopathological hallmarks of AD are the combined presence of two proteinaceous aggregates: extracellular neuritic (Aβ-containing) plaques and intraneuronal neurofibrillary tangles. Neuritic plaques are composed of a central core containing Aβ protein, surrounded by clusters of dystrophic axons, dendrites, and glia. In addition to brain parenchyma deposits, Aβ aggregates can be found on the walls of the leptomeningeal, cerebral cortical, and cerebellar blood vessels. Neurofibrillary tangles consist of paired helical filaments, formed by hyperphosphorylated tau protein. Cerebral amyloid angiopathy is correlated with AD pathogenesis and may lead to vascular rupture and multiple lobar hemorrhages (42).

In vascular dementia, multiple cerebral infarcts are visible upon inspection of the brain. Pathology associated with vascular dementia and AD frequently coexists (76). To diagnose vascular and not Alzheimer's dementia, there needs to be more vascular pathology than tangles and plaques.

Lewy Body disease histopathology shows the characteristic intracellular Lewy Bodies pathological aggregations of α-synuclein in the cerebral cortex and subcortical brain regions. The presence of extensive plaques and tangles signifies "low likelihood" of the disease (48).

In 1892, Arnold Pick, a professor of psychiatry at the University of Prague first described cases of striking frontal and temporal lobe atrophy in the brains of dementia patients without memory impairment. Twenty years later, Alzheimer was able to visualize microscopic silver-sensitive intraneuronal inclusions (Pick Bodies) and ballooned cortical neurons. For much of the 20th century, "Pick's disease" was synonymous with FTD.

The clinical syndrome FTD is caused by frontotemporal lobar degeneration (FTLD). Although distinguished on gross pathology by the selective degeneration of frontal and anterior temporal lobes, FTLD is histopathologically heterogeneous. Pick bodies do not have to be present to make the diagnosis. Specific FTLD subtypes are classified according to one of three abnormal protein inclusions, which are presumed to be pathogenic or most characteristic. These are based on tau (FTLD tau), TAR DNA-binding (FTLD-TDP), or fused in sarcoma protein (FTLD-FUS) (69). As of now, no correlation has been made between the pathological and clinical subtypes.

MND-HIV neuropathology is designated as HIV-encephalitis (HIVE). HIVE is characterized by synaptic loss and dendritic simplification in pyramidal neurons, loss of calbindin-immunoreactive interneurons, focal or diffuse myelin loss, widespread reactive astrogliosis, the accumulation of perivascular macrophages, and, in particular, formation of multinucleated giant cells and microglial nodules in central white matter and deep gray matter. Neuroimaging and pathology show white matter disruption in intercortical and cortico-striatal pathways. Hippocampal damage is also found and may relate to inhibition of neurogenesis in that structure (77).

2.3.5. Clinical Picture

Characteristic of the neurodegenerative dementias, Alzheimer's disease (AD) is a slowly progressive disorder with no fixed events that define its onset (64). Often, clinicians do not recognize dementia until the middle to later stages of disease. The typical AD patient is diagnosed 32 months after symptom onset (78). There are many reasons for missing early signs and symptoms of dementia. Patients' social skills are intact and they lack awareness of cognitive and functional problems. Knowledgeable informants are not always present at medical appointments. It can be a clinical challenge to identify transition points for individual patients from normal to abnormal function. For these reasons, clinicians need to be aware of the increased age-related risk of cognitive impairment and attuned to the subtle clinical signs. Common early medical presentations of cognitive impairment are unexplained weight loss or a previously stable patient who becomes unable to manage a medical illness and to follow advice regarding diet, exercise, keeping appointments, and completing paperwork. Failure to self-administer medications accurately is one of the earliest, most reliable, most culturally independent signs of mild dementia (79).

A Veteran's Administration study showed benefits of brief cognitive screening in veterans aged 70 or older who had not previously been diagnosed with cognitive impairment. Twenty six percent of veterans failed the screen, and of those who received further evaluation, 93% were diagnosed with cognitive impairment, including 75% who met criteria for dementia (80).

Making the diagnosis of dementia is extremely important. With the demographic shift toward an aging population in the USA, the prevalence of dementia will increase over the coming decades. The disease has significant consequences for the individual, families, medical system, and society as a whole. Families are significantly distressed by obvious lapses in performance and personality changes. They may attribute difficult behavior to willfulness, indifference, laziness, and passive aggression. They can be frustrated and angry with the patient but are relieved when an alternative reason is given for the distressing behavior. Caregivers require education and support for the difficulties of caring for a person with cognitive, psychological and behavioral disturbances. Social isolation with associated physical inactivity, boredom, agitation, and depression can be recognized and modified if the diagnosis is made.

Drivers with dementia can threaten public safety. Safe driving capability is questionable when family members refuse to be passengers, there is a history of crashes or traffic citations, presence of aggressive or impulsive personality characteristics, and examination findings of cognitive impairment. A patient will likely insist that he has always been a good driver but self-report is not an accurate predictive factor of safe driving (81). Persons with moderate–severe dementia can inadvertently start cooking fires, take unsafe risks using electrical equipment, firearms or power tools and be prey to predatory financial scams. Dementia can also affect medical decision making capacity and the ability to adhere to treatment recommendations. If dementia is diagnosed early, patients can have the opportunity to participate in financial and legal planning, and complete Advance Directives.

An accurate history of symptom onset and course is critical to diagnosing dementia. Because patients can be unaware of their symptoms, it is essential for the clinician to obtain corroborative history from a knowledgeable informant. An important clinical question is, has he or she always been like this or is this a change? Is the change sudden or has it developed gradually? Are the problems getting better, worse or staying the same? A clinician attuned to executive function can easily note any changes in the patient's ability to manage medical problems and medications. There is reason for concern if a previously well-managed problem such as hypertension becomes hard to manage, a patient cannot keep track of appointments or medications are no longer refilled on time. Other signs of executive dysfunction involve not paying bills, trouble shopping and cooking and difficulty with using tools. With visuospatial dysfunction, the patient may get lost driving in familiar locations or, in later stages of dementia, may wander off and be found by neighbors or police. If new onset perceptual disturbances are present, a description of the visual hallucinations or delusions can assist in diagnosis. Visual hallucinations in dementia with Lewy Bodies occur early and include well-formed and detailed figures of small children or animals. Delusions in AD usually occur in the moderate stage of the disease and are related to memory loss. A patient cannot find his/her wallet and thinks it has been stolen. A spouse is no longer recognized, so he/she must be an imposter.

The clinician can learn a great deal from the mental status examination. Patients with cognitive impairment can have poor hygiene or dress inappropriately for the weather, such as wearing short sleeves and slippers in the middle of a Minnesota winter. Inability to follow social conventions and cues may be a sign of frontal lobe dysfunction. Inappropriately disinhibited patients can stand too close to or attempt to kiss the clinician, or start touching objects around the office. Affect can appear labile or unusually disengaged and apathetic. Pathological affect occurs when the patient appears to laugh or cry without endorsing correspondingly elevated or depressed mood. The clinician can easily evaluate language by listening to how patients talk about things they are experts in, such as their personal history. Does the description of their previous line of work or a lifelong hobby make sense or is it hard to follow? Note the presence of word finding difficulties, paraphasic errors (substitution of one word, sometimes nonsensical, for a correct word), or empty speech (use of many words which communicate little).

Examining other cognitive domains is easy and straightforward. Serial cognitive examinations over time can capture progressive decline. As mentioned in the delirium Sect. 2.2.5 above, documenting a patient as "AOX3" provides little useful information about cognition. Brief but effective cognitive examinations cover attention, short-term memory (recall), and executive function.

Note if the patient is paying attention to you or has a decreased level of consciousness or is distractible. The Mini-Cog (18, 19) is a well-validated screening tool that takes under 2 minutes to complete. The patient is given three words to remember, a distraction task (draw a clock, set hands at 11:10) and is then asked to recall the three words. In the case of difficulty with recall or clock drawing, a more focused functional history and further cognitive assessment is indicated.

A focused neurologic examination will pick up signs associated with parkinsonism or other movement disorders or focal deficits that may indicate a cerebral lesion. "Frontal release signs," such as suck and snout reflexes, are nonspecific and will occur in most dementias late in the disease course.

A good history and examination are necessary and often sufficient to provide the clinician with enough information to diagnose a specific dementia; but early in the disease presentation, the clinical picture can be unclear. It is normal for elderly patients to have trouble remembering names and find it harder to keep track of things to do. Although there may be word-finding difficulties, the cognitively intact elder usually can recall the word with a cue, or after some time has passed. Solving unfamiliar problems and shifting mental gears may take more time and effort. Early Alzheimer's disease often presents with irretrievable word finding difficulties and poor short-term memory. There is trouble with getting lost driving in familiar places. The ability to keep track of finances deteriorates. These early cognitive changes can lead to mood changes, apathy, or anxiety. Symptoms and function gradually worsen over time.

Persons with dementia with Lewy Bodies have cognitive and perceptual problems, and develop motor and autonomic disturbances. Visual hallucinations occur in the early stages of the illness, and memory is initially less affected than attention, executive function, and visuospatial dysfunction (48).

Because of prominent psychological and behavioral changes, the behavioral variant frontotemporal dementia (bvFTD) patient is often brought to a psychiatrist for evaluation. According to diagnostic criteria ((54)—see Table 2.5), bvFTD patients will show early symptoms of at least three of the following changes: behavioral disinhibition (socially inappropriate behavior, loss of manners or decorum, impulsive, rash, or careless actions), apathy or inertia, loss of sympathy or empathy (diminished response to others' needs and feelings and diminished social interest, interrelatedness, or personal warmth), perseverative, stereotyped or compulsive/ritualistic behaviors, hyperorality, and dietary changes (altered food preferences especially sweet craving, binge eating, and increased consumption of alcohol or cigarettes and oral exploration or consumption of inedible items). Neuropsychological testing will show executive deficits with relative sparing of episodic memory and visuospatial skills. Diagnosis is made by observation or history provided by a knowledgeable informant.

2.3.6. Clinical Course

The course of the degenerative dementias is progressive and fatal. Initial presentations have been noted in Sect. 2.3.5, clinical picture. Global cognitive impairment is characteristic of all the dementias in their severe stages.

TABLE 2.5. Diagnostic criteria for possible behavioral variant frontotemporal dementia.

Progressive deterioration of behavior and/or cognition by observation or history
Persistent or recurrent symptoms of three of the following:
A. Early behavioral disinhibition with one of the following:
• Socially inappropriate behavior
• Loss of manners or decorum
• Impulsive, rash, or careless actions
B. Early apathy or inertia
C. Early loss of sympathy or empathy with one of the following:
• Diminished response to other people's needs and feelings
• Diminished social interest, interrelatedness, or personal warmth
D. Early perseverative, stereotyped, or compulsive/ritualistic behavior with one of the following:
• Simple repetitive movements
• Complex, compulsive or ritualistic behaviors
• Stereotypy of speech
E. Hyperorality and dietary changes with one of the following:
• Altered food preferences
• Binge eating, increased consumption of alcohol or cigarettes
• Oral exploration or consumption of inedible objects
F. Neuropsychological profile, with all of the following:
• Deficits in executive tasks
• Relative sparing of episodic memory
• Relative sparing of visuospatial skills

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Alzheimer's disease course progresses gradually, sometimes with brief plateaus, from mild to severe dementia to death. Factors that accelerate the decline are autosomal dominant familial type, presence of APOEε 4 allele, significant vascular disease, other medical comorbidities, presence of behavioral and psychological symptoms, and antipsychotic medications. The mean survival after diagnosis is approximately 10 years, although some individuals live as long as 20 years with the disease (1).

In the middle stages of the disease, patients require more assistance with instrumental activities of daily living such as finances, medication management, driving, and cooking. Behavioral and psychological symptoms are common, affecting up to 90% of patients (82). Sleep disturbances and "sundowning," (symptomatic worsening in afternoon and evening) will occur. Agitation and aggression often result in patients being brought to medical attention. Aggression, sleep–wake cycle disturbances, and delusions cause significant caregiver distress.

Persons with late stage Alzheimer's disease can have difficulty ambulating, dysphagia, myoclonus and seizures. They lose the ability to process information from the environment and may stop recognizing family members. Bowel and bladder control are lost. Most patients will be institutionalized at this point because the mental and physical demands of providing care 24 hours a day, 7 days a week exhausts even the most determined and resourceful families. End stage individuals are eventually mute and bedbound. Death most commonly results from aspiration and infection (1).

The course of DLB is progressive disabling cognitive and motor impairment. Although executive dysfunction and visual hallucinations are prominent early neuropsychiatric symptoms, memory impairment becomes more evident as the disease progresses (48).

Over time, impulsivity wanes and apathy is the main clinical finding in bvFTD. Decline is relatively rapid. In one sample, the mean time between onset and death was 7.8 years, with a standard deviation of 3.9 years. A small subset of patients does not decline clinically over time (54).

2.3.7. Laboratory/Imaging

Although clinical criteria are used to diagnose a specific dementia type, laboratory testing and neuroimaging can rule out potential comorbidities. The 2001 American Academy of Neurology practice parameter for diagnosis of Alzheimer's disease (83) recommends obtaining blood tests and, when clinically indicated, neuroimaging. Blood tests are useful in dementia to exclude treatable medical comorbidities. According to these guidelines, syphilis and HIV serological tests should be considered in high-risk populations and when there are suggestive clinical features. (More recent guidelines from the American College of Physicians endorse universal HIV screening in adults to age 75, i.e., regardless of cognitive status (84).)

Central nervous system imaging is worthwhile with focal neurological symptoms on examination, early onset or atypical presentation. "Generalized atrophy," loss of gray matter or "small vessel ischemic disease" are common findings in cognitively normal seniors and do not necessarily correlate with dementia. Increasingly, structural or functional imaging findings are part of research criteria to define probable as opposed to possible dementia; but clinical use of imaging modalities to diagnose specific dementias remains more limited.

There is considerable research interest in disease biomarkers, including Aβ protein deposition and downstream neuronal injury. Amyloid imaging on brain positron emission tomography (PET) scans and reduced levels of Aβ in the CSF may have diagnostic value (1), but are not yet reliable enough to be used clinically. In the future, biomarker evidence is expected to enhance the pathophysiological specificity of the diagnosis (41).

Genetic testing is recommended for symptomatic patients with early onset AD, individuals with a family history of dementia with one or more cases of early onset AD and individuals with a relative affected by a known mutation of APP, PSEN1, or PSEN2 (42).

Neuroimaging evidence is a criterion for probable bvFTD. Present are frontal and/or anterior temporal atrophy on MRI or CT or frontal and/or anterior temporal hypoperfusion or hypometabolism on PET or SPECT (51).

There are no clear neuroimaging criteria for major neurocognitive disorder due to HIV (MND-HIV). Volumetric and structural magnetic resonance and diffusion tensor imaging demonstrate cortical/subcortical atrophy and white matter abnormalities in HIV-infected individuals. Reduced basal ganglia volume is associated with cognitive impairment on neuropsychological testing. As compared to HIV-seropositive individuals without cognitive impairment, subcortical volume loss can be seen in individuals with MND-HIV. Functional imaging modalities such as MR spectroscopy and positron emission tomography also show white matter abnormalities (77).

2.3.8. Differential Diagnosis

Longitudinal assessment of a patient's cognition and function is important to differentiating dementia from other mental disorders. The decline from baseline function and performance distinguishes dementia from mental retardation. Not uncommonly, cognitive impairment can be a feature of major psychiatric disorders (such as depression or schizophrenia) just as psychiatric

symptoms can be present in dementia. In major psychiatric disorders, cognitive deficits, if noticed, are generally less evident than mood, psychotic or anxiety symptoms. Patients with psychiatric illness have variable performance on cognitive tests, with poor effort and insistence that they cannot do items on which they ultimately perform well.

Patients who present with concerns about memory but have intact function are often depressed or anxious, although MCI should be considered, since as many as one third will go on to develop dementia over 2 years (65). "Pseudodementia" is a condition where a depressive disorder presents with prominent confusion that clears when the depression is treated. These patients should receive regular cognitive assessments. A majority of these develop dementia over 5–7 years (85).

Dementia often presents as depression or anxiety. A family member becomes apathetic and looks depressed but does not endorse sadness and finds pleasure in fun situations. Or, without an anxiety disorder history, he/she appears anxious when in an environment where the cognitive demands of the situation are too overwhelming. Demented patients will have cognitive, behavioral and motor disturbances and respond poorly, if at all, to psychiatric medications or ECT.

Persons with dementia can display pathological laughing and crying, also referred to as pathological affect or pseudobulbar affect. These brief, unprovoked stereotyped affective displays that occur without voluntary control or modulation are often mistaken for primary psychiatric illness (56). Determining the patient's prevailing mood will differentiate the dysregulated affect of dementia from mania or depression. For example, if the person does not appear depressed most of the time and, when redirected, can easily switch from a teary outburst to an expression of joy, the diagnosis is not likely to be depression.

Apathy can be a symptom of depression or a cognitive syndrome commonly associated with dementia. In DSM-5, symptoms of depression that suggest apathy are loss of interest in activities and psychomotor retardation. The apathy frequently associated with AD, vascular dementia, the subcortical dementias and bvFTD (86) is often mistaken for depression by psychiatrists (87) and other clinicians. Apathy syndrome is defined as diminished motivation (88) without the sadness and considerable emotional distress that accompany depression.

To complicate matters, cognitive impairment and depression often coincide in neurodegenerative disease, and in clinical situations, it is often difficult to distinguish between the two. In Parkinson's disease, depression worsens executive function, with poorer mental set shifting and response inhibition evident on neuropsychological testing. Treatment with an SSRI can improve cognitive performance independently of effects on depressive symptoms (89).

Examination of psychiatric comorbidities in bvFTD shows that psychosis is rare (55) and affective lability does not have the pervasive changes in mood and neurovegetative signs characteristic of a mood disorder. Sociopathy or addictive disorders developing in late life may be signs of bvFTD (57).

Patients with dementia are at higher risk for delirium and depression, so care must be undertaken to determine overlap and treat appropriately. Knowing the person's baseline and obtaining corroborative history are essential. An acute change in behavior in a demented person is delirium until proven otherwise.

Persons with dementia with Lewy Bodies (DLB) or delirium can exhibit cognitive fluctuations and attentional deficits. DLB can be differentiated by the presence of Parkinsonism, REM sleep behavior disorder and autonomic instability as well as symptom worsening, not recovery over time. Hallucinations in DLB are usually well formed and detailed. Differentiating DLB from AD involves reviewing the neuropsychiatric symptom profile. The difference between DLB and Parkinson's disease dementia is based on history; cognitive symptoms in DLB occur at least one year before the onset of motor symptoms (48).

Both dementia and schizophrenia are associated with executive dysfunction. In fact, Emil Kraepelin first called schizophrenia by the term *dementia praecox.* Psychosis in dementia usually involves visual hallucinations and delusions related to memory loss (theft, agnosia, unfaithfulness). Psychosis in schizophrenia often involves bizarre, paranoid delusions and auditory hallucinations. Although schizophrenia usually has an onset between the late teens and late 30s, a small proportion of patients will have an onset later in life.

Amnestic disorder is an impairment of only one cognitive domain: memory. Although there are many plausible causes, alcohol is the most important cause via thiamine deficiency and the induction of a delirium (Wernicke's encephalopathy) followed by persistent amnesia (Korsakov's psychosis). Alcoholic dementia is also characterized by memory impairment, with a clear history of alcohol abuse/dependence. Expectation is that memory and function will stabilize after sobriety is achieved.

2.3.9. Treatment

Pharmacological strategies in dementia have focused on neurotransmitter replacement and modulation for the treatment of cognitive, behavioral and other neuropsychiatric symptoms. These therapies are only modestly and often inconsistently effective. The concept of dementia "treatment" must be broadened to include psychosocial interventions. The most effective treatments are those that promote safety, independence and better quality of life (80). The demented patient is no longer able to adapt the environment to meet his needs so the environment itself needs to be adapted. Caregivers can easily become exhausted and depressed. Providing a safe environment and the continuous education and support of caregivers are the most effective ways of managing problematic behaviors and safety issues.

Caregivers need to know that dementia progression means that the symptoms and behaviors change over time and that behavioral and environmental interventions will need to change as well. At any stage of the illness, safety issues involving money, medications, vehicles, home appliances, tools and firearms need to be addressed. Adaptation of facilities at home should be planned to minimize confusion and falls. Patient enrollment in adult day programs can provide physical activity, social interaction, and engagement in mentally stimulating activities; as well as respite for caregivers. Caring for a person with moderate-severe dementia requires consistent attention and the ability to redirect agitated or unsafe behavior. The patient benefits when the caregiver's own need for time away is met. The use of advocacy organizations for education, resources, and support is crucial (90). Because of caregiver stress and patient's memory problems, the clinician may need to repeat essential information over the course of treatment.

For the clinician, an individualized approach to comorbid conditions and simplification of medication regimens is essential. There are a few helpful rules of thumb. Consider dementia the organizing principle of care for patients. Be aware that the keys to good care are to preserve function, maximize quality of life, and help patients identify and meet goals. Effects on patient function and dementia progression should be considered in every care decision, including the treatment of comorbid illnesses (91). Ongoing monitoring and modification of care goals and treatments is necessary as the disease progresses.

The currently available medications used for AD enhance cholinergic or inhibit glutamatergic neurotransmission. They offer symptomatic benefit in cognition, function and behavioral outcomes. Maximum benefit appears to be gained early in treatment, although donepezil, a cholinesterase inhibitor, has been shown to have benefits in moderate-to-severe Alzheimer's disease as well (92).

Cholinesterase inhibitors (donepezil, rivastigmine, galantamine) are the mainstay of cognitive treatment. In clinical trials, they consistently show a modest benefit on cognition global outcome and function when compared to placebo. They do not modify disease progression but appear to stabilize cognition and function for the first 6–12 months of treatment. These medications may have some benefit in treating dementia related apathy and agitation. They are generally well tolerated but can cause side effects such as gastrointestinal disturbance, anorexia and sleep disturbances. Rare, severe side effects include bradycardia and syncope. Cholinesterase inhibitors do not alter the conversion of mild cognitive impairment to AD (93). However, they can be useful in the Lewy Body diseases (DLB and Parkinson's dementia), where visual hallucinations often decrease in frequency and intensity in response to cholinergic treatment.

Memantine, an *N*-methyl-D-aspartate (NMDA) receptor antagonist, is FDA approved for moderate-to-severe AD. The proposed mechanism of action is neuronal protection against glutamate-mediated excitotoxicity. It has been shown to have modest benefit in cognitive performance and global function for AD and possibly vascular dementia. It may be useful in preventing and treating agitation, aggression, irritability and psychosis (94). It is usually well tolerated. Side effects can include headache and gastrointestinal disturbance. There may be additive cognitive benefits to combining a cholinesterase inhibitor and memantine, although this is not a consistent finding in the medical literature. In Britain, analysis of data from the National Health Service prompted the recommendation to use a cholinesterase inhibitor but not memantine, unless there is a contraindication or intolerance to a cholinesterase inhibitor (95).

There are many studies underway to find treatments for AD, most targeting Aβ, including drugs that reduce Aβ production and immunotherapy to remove Aβ. Other strategies under investigation include using compounds that reduce tau hyperphosphorylation, as well as enhancing brain-derived nerve growth factor (BDNF) or potentiating the effects of caffeine and exercise (42).

Difficult, distressing, and dangerous behaviors often accompany dementia and effective medical treatment is elusive. Human behavior is complex and difficult to predict. There are reasons why a person with dementia may be agitated, pacing, yelling, weeping, throwing objects, or physically assaultive. But dementia impairs the ability to communicate what is wrong, so it is up to the caregiver to figure out where the problem lies. Treating common problems such as pain and constipation can be very effective at calming behavior. Providing caregiver education, adjusting the environment to meet the patient's needs and offering reassurance and redirection are more effective than using medication. When psychological and environmental approaches are not possible or have proven ineffective and the behaviors are dangerous and distressing, antipsychotic medications are the mainstay of treatment (96). They have modest benefits—18% over placebo (97)—but significant potential side effects, including falls, stroke and death. They are most effective for short-term treatment of psychotic symptoms in dementia. Antipsychotic discontinuation studies in Britain have shown increased socialization, decreased mortality and no significant increase in agitation when the antipsychotic is stopped (98). These drugs should be avoided in Lewy body disease due to worsening motor symptoms and increased fall risk. There is sparse literature supporting the use of other medications for agitation; including SSRIs, trazodone and anticonvulsants. Giving benzodiazepines to demented patients should be avoided, because of potential for disinhibition, falls, and adverse effects on cognition (82).

There is no specific medication for bvFTD. Cholinesterase inhibitors are ineffective and may cause increased agitation and irritability. SSRIs are commonly used for controlling symptoms and modulating behavior, based on the consideration that the depression, aggression and impulsivity seen in bvFTD are examples of serotonergic dysfunction. SSRIs may also be effective in ameliorating disinhibition, depression, compulsions, and carbohydrate craving. Trazodone (a mixed serotonin agonist/antagonist with serotonin reuptake activity) has been found useful to treat distressing behaviors in bvFTD (69).

For treatment of HIV related neurocognitive disorders, psychostimulants have demonstrated efficacy, although concerns for abuse liability may limit use in a population that includes substance abusers (75).

2.4. Mental Disorders Due to Another Medical Condition

A conceptual theme that underlies this chapter is that mood, anxiety, or psychotic symptoms and disordered behavior can be interpreted, depending on the clinician's perspective, as primarily psychiatric or medical. Mental disorders were incorporated into psychiatric nosology in 1972, when the so-called Feighner criteria (99) included "secondary depression" that could arise in the context of a life threatening or incapacitating medical illness. The notion of "organic" illness was operationalized eight years later in DSM III, (100) which designated four organic syndromes: hallucinosis, delusional disorder, affective and personality disorders. Later iterations of the DSM considered psychiatric symptoms arising from a medical condition as "secondary" disorders, than those "due to a general medical condition." The "organic" designation was eliminated in DSM-IV-TR (101). DSM-5 closed the gap between psyche and soma by referring to this category as "mental disorders due to *another* medical condition" (emphasis added), perhaps looking forward to the time when psychiatric pathophysiology is better described.

Descriptions of the different disorders are listed in the DSM under the corresponding psychiatric diagnosis. This chapter section combines these disorders under one heading and reviews the symptoms of psychosis, catatonia, mood and anxiety disorders, and personality change that are caused by other, detectable medical illnesses. Following convention, *secondary* is the term that will be used for the mental disorders due to another medical illness.

2.4.1. Definitions and General Observations

Recognition of mental disorders due to another medical condition requires several judgments on the part of the diagnostician. A specific medical condition needs to be identified, based on the history, physical examination, and/or laboratory finding. As with delirium, there are many possible conditions but some have known physiological mechanisms that are well supported by the medical literature. There are no infallible guidelines for diagnosis (1), but some helpful clues exist. First, there must be no preexisting psychiatric diagnosis. Second, there should be a temporal association between the medical illness and psychiatric symptoms. That is, the psychiatric symptoms should coincide with the onset and course of the medical condition, arising shortly after the onset and remitting near the time that the medical condition is effectively treated. This temporal sequence is not always the case. Mood symptoms often precede the motor disturbances in Parkinson's disease (89). In central nervous system systemic lupus erythematosis, mood and psychotic symptoms can be present months before other manifestations of illness. Alternatively, psychosis has long been known to be a late complication of chronic epilepsy. The latter mechanism may be similar to seizure kindling: psychotic episodes may beget psychotic episodes (102). Associations may be bidirectional: the risk of developing depression appears to be increased in patients who suffer from preexisting migraine headaches and a history of depression appears to increase the risk of developing migraine. Physiological adjustment to and compensation for most illnesses result in systemic changes that cause symptoms associated with depression. For example, changes in the hypothalamic–pituitary–adrenal axis or increased production of pro-inflammatory cytokines causes vegetative symptoms such as fatigue or anergy that are common to being sick or depressed. The mental disorder and medical condition may share common pathophysiology. Catecholamines, platelet abnormalities, impaired immune function, and increased cytokines appear to play a role in both depression and coronary artery disease (103).

A third consideration for detecting a medical etiology is an atypical psychiatric presentation, with either onset outside of the expected norm for age, or symptoms that do not fit the profile for the primary psychiatric illness. For example, onset of schizophrenia and anxiety disorders becomes less common with increasing age. Appearance of psychosis after age 40 should prompt a thorough neurological examination, laboratory and imaging studies. Consideration of substance abuse or medical illness should accompany the workup of new onset of anxiety after the second or third decade. Hallucinations that are visual or olfactory instead of the more common auditory hallucinations in schizophrenia can indicate a secondary cause. Sub-threshold syndromes—several symptoms of depression or an unusually long duration to worsening of panic symptoms, for example—may be a clue to an association between a medical condition and a mental disorder.

Prior episodes of mental illness and a strong family history would suggest caution about attributing symptoms to a particular medical condition, regardless of how plausible the connection might appear. In the presence of a well-defined preexisting mental illness, the medical illness associated with a mental disorder should not be considered the primary cause of the symptoms.

The mental disorders due to another medical condition are relatively rare disorders that occur primarily in a medically ill population. Therefore, it is often difficult to determine population prevalence, with depression a notable exception. To link a medical illness to depression, which has a roughly 10% lifetime prevalence, the rate of depression associated with a particular medical condition should rise above the base rate.

It should be emphasized that depression is not the inevitable outcome of severe medical illness. People have an amazing capacity to show resilience in the face of debilitating disease. There may be an adjustment to the illness, with the stress that comes from the loss of a "normal" life. Persons who are "sick and tired of being sick and tired" may become demoralized; but their mood returns to normal as their medical illness improves. Demoralization does not have the pervasive hopelessness or anhedonia associated with a depressive disorder.

Exclusionary criteria for mental disorders due to another medical illness include a primary psychiatric diagnosis or a neurocognitive disorder, especially delirium. As with all other psychiatric syndromes, the disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.

2.4.2. Psychotic Disorder Due to Another Medical Condition

Hallucinations or delusions dominate the clinical picture of psychotic disorder due to another medical condition. The parallel primary psychiatric disorders are schizophrenia and related syndromes. Coincident occurrence of psychotic symptoms with a medical illness, onset after age 40 and atypical features are clues to a secondary psychotic disorder. At any age, prominent visual, tactile or olfactory hallucinations suggest a medical cause. Psychosis in the context of inattention and other cognitive impairments indicates delirium. DSM 5 places medication-induced psychosis, such as that found with high dose steroid use, in its own category.

The known pathophysiology of secondary psychotic disorders includes multiple systems: neurological, endocrine, toxic metabolic, and autoimmune. Psychosis can be present with neoplasms, cerebrovascular disease, Huntington's disease, multiple sclerosis, epilepsy, auditory or visual nerve injury or impairment, deafness, migraine, and central nervous system infections. Temporal lobe seizure activity can produce olfactory hallucinations and religious delusions. Untreated endocrine disorders associated with psychosis involve thyroid, parathyroid and adrenocortical systems. Associated toxic metabolic conditions include hypoxia, hypercarbia, hypoglycemia, fluid or electrolyte imbalances, hepatic or renal disease. The clinical presentation of CNS systemic lupus erythematosis and other vasculitidies can include psychosis. Nervous system dysfunction associated with the acute porphoryias can include hallucinations and agitation.

Symptomatic treatment with antipsychotic medication is recommended if treatment of the medical condition is not sufficient or the delay in response to medical intervention puts the patient/others at risk.

2.4.3. Catatonic Disorder Due to Another Medical Condition

Catatonia is a relatively rare psychiatric condition characterized by stupor (no psychomotor activity; not actively relating to the environment), catalepsy (passive induction of a posture held against gravity), extreme negativism or mutism, peculiarities of movement (posturing, mannerism, stereotypy, grimacing), echopraxia (mimicking another's movements), and echolalia (mimicking another's speech) (1). Sometimes patients show excessive purposeless activity. Catatonia is a serious problem that can become complicated by pneumonia and urinary tract infections, deep vein thrombosis, pulmonary embolism, and death. Although it is more frequently associated with primary psychiatric conditions, catatonia can be seen in neurological (encephalitis, head trauma, cerebrovascular disease, central nervous system neoplasms) and metabolic conditions (hypercalcemia and diabetic ketoacidosis) (104). As with all the secondary disorders, the differential diagnosis includes delirium. Psychosis may be the common symptom that links catatonia and schizophrenia. Unfortunately, treatment with antipsychotics can produce a medication-induced dystonia or cause neuroleptic malignant syndrome, which can mimic catatonia. Benzodiazepines and electroconvulsive therapy (ECT) can effectively treat catatonia, and are the recommended therapies.

2.4.4. Mood Disorders Due to Another Medical Condition

The DSM-5 lists depressive, bipolar and related disorders due to another medical condition under their respective mood syndromes. Clinical features mirror those of mania or depression: a prominent and persistent period of abnormally elevated, expansive or irritable mood, and abnormally increased activity or energy (mania), or depressed mood or markedly diminished interest or pleasure in all or almost all activities (depression). History and longitudinal course help differentiate a primary from a secondary mood disorder. In the latter, the mood disturbance usually appears within a month of the medical condition.

Thyroid disorders, both hypothyroidism and hyperthyroidism can include mood symptoms and complicate affective illness (1). Cushing's disease, traumatic brain injury, and multiple sclerosis can appear with a bipolar or depression presentation. There are clear associations between depression and neurodegenerative illnesses such as Parkinson's disease and Huntington's disease. Stroke-related depression has a prevalence of 29%, some of which represents a recurrence of preexisting illness. The major predictor of new onset depression is stroke related disability; other factors include cognitive impairment, stroke severity, lack of social and family support, and anxiety. The risk of post-stroke depression is not affected by the location of the lesion (105). New onset mania, a very rare consequence of stroke, is associated with right hemisphere lesions. The typical symptoms of mania usually occur within days of the stroke (106).

Substance induced depression has its own category in DSM-5. The depressive symptoms are associated with the ingestion, injection or inhalation of a drug or toxin and persist beyond the direct physiologic effects of the substance, including withdrawal. There are few prospective controlled trials examining the association of depressive symptoms with use of a medication and evidence of causality is difficult to determine. According to the DSM-5, the long list of medications implicated in medication-induced depressive disorder includes: antiviral agents (efavirenz), cardiovascular drugs (clonidine, guanethidine, methyldopa, reserpine), retinoic acid derivatives, antidepressants (107), anticonvulsants, anti-migraine agents (triptans), antipsychotics, hormonal agents (corticosteroids, oral contraceptives, gonadotropin-releasing hormone agonists, tamoxifen), and immunological agents (interferon) (1).

2.4.5. Anxiety Disorder Due to Another Medical Condition

Anxiety disorders due to another medical condition are specified in DSM-5 as being predominantly associated with panic attacks or anxiety and obsessive-compulsive symptoms. These subtypes reflect prominent types of anxiety disorders. In general, primary anxiety disorders tend to arise in childhood to early adulthood and are more frequent in women than in men. Anxiety symptoms that present after age 45 years or include atypical panic symptoms (vertigo, loss of consciousness, loss of bowel or bladkder control, slurred speech, amnesia) are more likely to be related to another illness or medications. In secondary anxiety, gender prevalence is equal. Cardiovascular disease and respiratory conditions, including pulmonary embolus, are commonly associated with anxiety. Symptoms can present in neurologic illness such as neoplasms, vestibular dysfunction, encephalitis, and seizure disorders. Rare conditions such as pheochromocytoma and porphyria have also been associated with anxiety.

Obsessive–compulsive disorder related to another medical condition involves prominent obsessions, compulsions, preoccupation with appearance, hoarding, or body-focused repetitive behaviors (e.g., hair pulling, skin picking). Striatal damage is a known physiological mechanism. PANDAS, pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection, is a controversial diagnosis that is characterized by sudden onset of obsessions, compulsions and/or tics in the absence of motor symptoms or arthritis following a Group A streptococcal infection (1).

The association between anxiety and vascular disease is bidirectional. Anxiety symptoms and stress increase both incident coronary heart disease and cerebrovascular disease. The association with coronary heart disease is especially strong in women. The connection between anxiety disorders and hypertension is unclear. Suggested mechanisms involve the effects of sympathetic nervous system and hypothalamic–pituitary axis hyperactivity along with altered sympathovagal control of the heart increasing the risk of cardiovascular disease and decreasing the threshold for cardiac ischemia, arrhythmias and sudden death (102).

Differential diagnosis of anxiety complicating medical illness includes depression (which often has anxiety as a symptom), medication intoxication and withdrawal, and delirium. Other primary psychiatric disorders in the differential include illness anxiety (worry not associated with a diagnosed medical condition) and adjustment disorders, which are merely associated with the stress of being ill (1).

Pending resolution of the medical condition, SSRI's and other antidepressants as well as benzodiazepines can effectively control secondary anxiety disorder symptoms. Benzodiazepines can cause respiratory depression and loss of protective airway reflexes; level of consciousness, ventilatory effort, and respiratory function should be monitored if this class of medications is used.

2.4.6. Personality Change Due to Another Medical Condition

Personality Change due to another medical condition is listed under the Personality Disorder category in DSM-5 but is not as well defined as the other secondary disorders. However, as its name suggests, features of Personality Change represent a new and different pattern of inner experience and behavior as opposed to the enduring patterns required for a primary personality disorder diagnosis. Specific Personality Change subtypes are labile, disinhibited, aggressive, apathetic, and paranoid. With the exception of the paranoid subtype, they show little relationship to primary personality disorders. Common manifestations of Personality Change include affective instability, poor impulse control, outbursts of inappropriate aggression or rage, marked apathy, suspiciousness, or paranoid ideation. The clinical presentation depends on the nature and localization of the lesion or pathological process. Personality change often accompanies traumatic brain injury, of which Phineas Gage, whose friends described him as "no longer Gage," is a prime example. It is associated with neurodegenerative disease, especially involving the frontal lobes. Right hemisphere strokes can trigger personality changes in association with unilateral spatial neglect and motor symptoms. DSM-5 allows the Personality Change designation in addition to a major neurocognitive disorder (dementia) diagnosis, if the personality change is a prominent part of the clinical presentation (1).

Treatment is similar to that of the dementias. A structured safe environment, acknowledgement and redirection, and caregiver education and support are the most effective treatments. SSRIs and antiepileptic drugs can help modulate aggression. Antipsychotics may attenuate paranoia. Lithium, buspirone, antidepressants, benzodiazepines, and β blockers have been used empirically with no clinical trials showing evidence of benefit.

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3
The Amnestic Syndrome

Afshan Anjum, M.D.*

Abstract This chapter focuses on the amnestic syndrome or an impairment in the ability to form new memories. The chapter first describes the history of amnestic disorder and background on memory and memory function. Descriptions of the four amnestic syndromes (Wernicke–Korsakoff syndrome, transient global amnesia, mild cognitive impairment, and hysterical amnesia) are then provided. Finally, the etiology, evaluation, and treatment of amnestic syndrome are described.

Keywords Amnesia · Memory · Transient global amnesia · Wernicke–Korsakoff syndrome · Mild cognitive impairment

3.1. Introduction

3.1.1. History

This chapter will focus on a medical rarity that is far more common in artistic renderings of amnesia than it is in real life. The importance of the amnestic syndrome in research is substantial as it is a single symptom impairment that provides rare views into the function of memory processes. The amnestic syndrome is defined simply by impairment in the ability to form new memories. There are usually other associated features, some of which may be quite striking, e.g., the patient's indifference to their deficit, though these features are secondary in prominence to the overwhelming deficits in memory. There is some disagreement about how much impairment in other domains distinguishes an amnestic disorder from a dementia syndrome. The memory defect is in "new learning" or "short-term" memory though some loss of remote memories is usual. Older memories tend to be protected and resistant to damage. Ribot's law, first articulated by the French psychologist Theódule Ribot in 1882, notes that amnesia affects memories in reverse order of their development—"The dissolution of memory is inversely related to the recency of the event (1)." Memories of recent events are most vulnerable; memories of events long ago are more resilient. The terms *anterograde* and *retrograde* memory are important here. Anterograde memory refers to the ability to lay down new memories and is sometimes called "recent memory" or new learning. Retrograde memory refers to the ability to recall previously learned material or prior experiences. Amnestic disorders are primarily disorders of anterograde memory though some component of retrograde memory loss is invariably present. Some (2) have argued that the retrograde impairment is quite prominent though detection of this deficit requires a more specialized approach to cognitive testing.

Memory disorders can be classified based upon phenomenology, etiology, and nosology. The Diagnostic and Statistical Manual of Mental Disorders (DSM-5) introduced a new category, neurocognitive disorders (NCDs) as a substitute for the dementia, delirium, and amnestic disorders in DSM-IV (3). While upholding the term delirium, the very familiar term dementia will not be a diagnostic entity. Neurocognitive disorders include dementias and purported early prodromal stages of dementias. The diagnosis of NCDs requires psychological testing. NCD is further differentiated into major and mild categories with major neurocognitive disorders including dementia and other debilitating conditions and mild neurocognitive disorders (mNCDs)

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A. Anjum, M.D. (✉)
Assistant Professor, Department of Psychiatry, University of Minnesota School of Medicine,
Minneapolis, MN, USA
e-mail: anju0001@umn.edu

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defined by noticeable decrease in cognitive functioning that goes beyond normal changes seen in aging. The new concept of NCD also allows the diagnosis of etiological-specific prodromal states of cognitive impairments.

3.1.2. Phenomenology of Memory

Memories can be described by their temporal occurrence or by their content.

3.1.2.1. Types of Memory

3.1.2.1.1. Temporal

The terms used to describe memory can be quite confusing and lacking in uniformity of use. For example, how short is the term in "short-term" memory? "Short-term" memory can be used to refer to immediate recall or repetition of a list (registration), to keeping that list in mind while focusing on another task (working memory), to memories of events from minutes prior, hours prior, or days earlier. Memory is most often defined temporally as in immediate, short term or long term or by its content (see Fig. 3.1).

Immediate memory, also known as working memory, attention span or registration, refers to the first grasp of information in its original apperception, e.g., the visualization of a license plate or hearing a telephone number. This information is retained only as long as one is actively attending to it. Once attention is diverted, e.g., when one stops looking at the license plate or hearing the telephone operator, the numbers are lost from recollection. To retain such information it must be passed to short-term memory where it is transformed to a symbol or semantic construct such as a word or number. Immediate memory involves parts of the prefrontal and parietal cortices but does not involve the limbic lobes.

Short-term memory is very much a limbic phenomenon. Here sensory information is encoded and initial consolidation of the sensory material into a symbolic representation begins. Further consolidation comes with rehearsing the new knowledge until the symbolic representation is formed (see Fig. 3.1).

Long-term memory refers to the enduring memory traces formed after consolidation is completed. Consolidation likely reflects a potentiation of neural circuits (see Fig. 3.1).

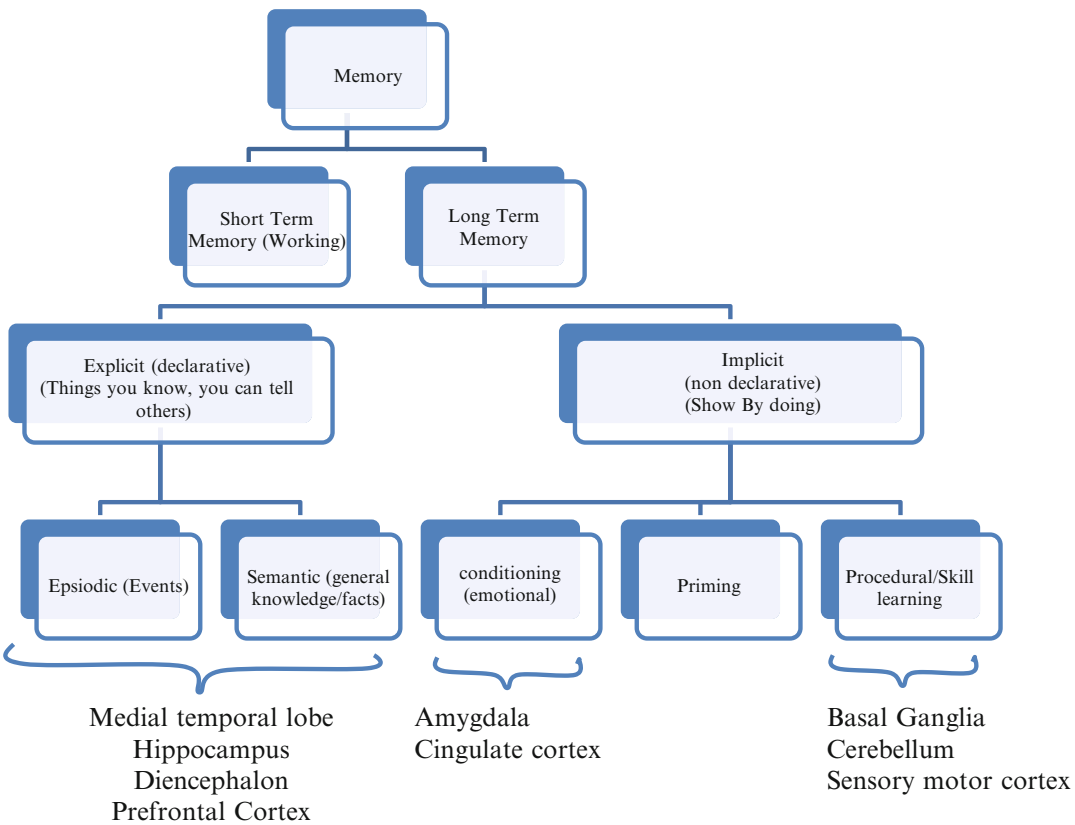

FIGURE 3.1 Classification of types of memory and the relevant brain regions involved.

3.1.2.1.2. Content

Content definitions of memory distinguish between declarative memory which requires a conscious effort (e.g., what is the capital of Idaho?) and non-declarative memories that rely upon unconscious retrieval of information (the association of fire to a burning smell).

Explicit and Implicit Memory

Explicit memory refers to the ability to *consciously* recollect facts and events (see Fig. 3.1). Explicit memory is sometimes known as a declarative memory and can be subdivided into semantic memory, the recollection of facts and rules, and episodic memory, the recollection of past events and circumstances. Implicit memory refers to information that is learned or recollected without conscious effort (see Fig. 3.1). Edouard Claparede (1873–1940), the French neurologist, provided an early description of a patient who illustrates the distinction between implicit and explicit memory. Claparede's patient suffered from a classical Korsakovian amnesia with little ability to learn new semantic information. She was unable to learn the name of the hospital in which she had been residing for many years, could not report the city she was in and could not recall her birthdate. She was able, however, to learn her way about the facility and to find her room from the dining room and other public areas. This demonstrates intact visuospatial learning. Claparede's famous experiment (which would not be approved by a contemporary IRB!) involved introducing himself to the patient with a handshake that disguised a sharp pin in his hand. After a short lapse in time, Claparede reintroduced himself to the patient who demonstrated no recognition of his face and no explicit recollection of having met him before. However, when he extended his hand with a handshake, the patient declined to take it, noting famously, "some people hide pins in their hands." Here we have learning without explicit knowledge of that learning and without semantic details, i.e., only the pain associated with the handshake is learned, not the name or face of the pain-inducing hand shaker.

Procedural memory is the non-conscious recollection of motor activities and skills (see Fig. 3.1). The motor skills of driving a car or hitting a golf ball rely upon procedural memory. These are almost "automatic" activities that do not require conscious effort. As noted above a different neuroanatomical circuit than that of new learning subscribes these memory functions and these memories are more resilient. Not infrequently, caregivers will report that an amnestic patient's driving skills are quite good though the patient cannot functionally drive because they cannot remember where they are going or how to navigate there (a failure of episodic memory) or they cannot recall the rules and etiquette of safe driving (a failure of semantic memory). Similarly, the amnestic golfer might hit true and strong strokes and putt evenly but will have great difficulty remembering whose turn it is, where his ball was resting, or with whom he golfed or even that he has golfed. Here the implicit mechanisms of procedural memory are carrying the amnestic's golf game.

3.2. Anatomy of Memory

3.2.1. Diencepalic vs. Hippocampal Amnesia: Korsakoff, Wernicke, and Milner

Korsakoff and Wernicke worked and wrote in the same decades of the late 19th century but neither they nor any of their contemporaries saw a connection between their descriptions of amnestic conditions. Decades later, there emerged reports of patients who presented with acute Wernicke's encephalopathy and then developed a chronic Korsakovian amnesia, demonstrating that the two syndromes represented different time points of the same condition. Not before the 30s, however, when cases of Wernicke's were described in non-alcoholic patients with gastric malabsorption, it was appreciated that the etiology was related to nutritional deficiency, namely insufficient thiamine or Vitamin B1. Damage to the diencephalon, meaning mammillary bodies and mesial thalamic nuclei, was identified as the underlying neuropathology. Amnestic disorders and Korsakoff's syndrome became virtually synonymous until the 1950s when Brenda Milner and her colleagues described amnestic patients like H.M. who had demonstrable pathology remote from the diencephalon. H.M. had intractable seizures for which he underwent bilateral surgical extirpation of the medial aspect of his temporal lobes, including at least the anterior hippocampi. Seizures were indeed relieved but he was left with a profound deficit in new learning with his other intellectual facilities largely remaining intact (4). In a landmark series of studies of H.M., the integral role of the hippocampi in formation of new memories was clearly demonstrated.

3.2.2. Anatomy and Memory Function

The roles of memory formation and memory storage are carried out in different structures. Memories are initially formed in the limbic memory system. They are temporarily stored in these structures but ultimately long-term storage requires other structures. Amnesia as noted above, is a failure in new learning or in the encoding of new information or the laying down of new memories.

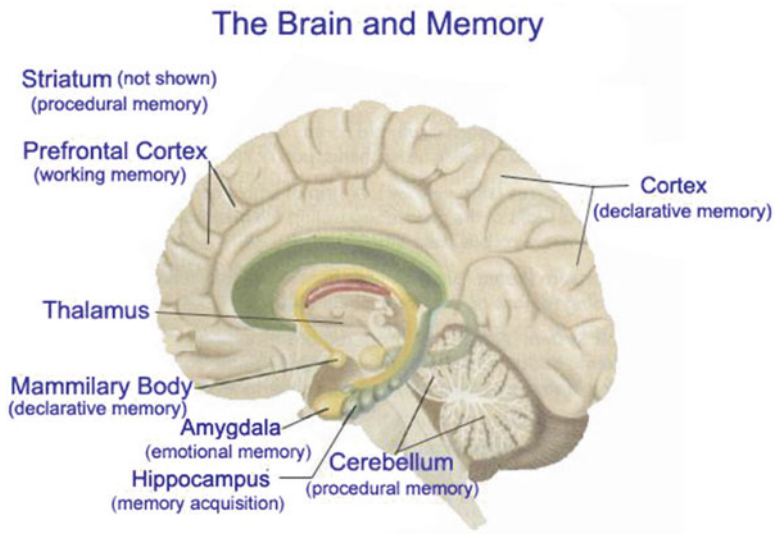

FIGURE 3.2. Anatomy of brain structures involved in memory. Reprinted with permission from Bionews Texas, http://bionews-tx.com/wp-content/uploads/2013/08/memory.jpg.

This is because amnestic syndromes derive from damage to the limbic structures subserving the encoding of new information—the laying down but not the storage of long-term memories (see Fig. 3.2). The structures most commonly involved are the hippocampus and/or the diencephalon as they are highly vulnerable to vascular compromise, anoxic injury, and head trauma.

The hippocampi have major roles in new learning (anterograde memory) but are not involved in long-term storage (retrograde memory) (see Fig. 3.2). The diencephalon includes the mammillary bodies, mammillothalamic tracts, medial dorsal thalamic nuclei, and the internal medullary lamina (see Fig. 3.2). While these structures certainly have a role in new learning that is inferred from the disorders that result from focal damage to these structures, the precise function of these structures in memory has not been determined as yet. Some have suggested that the mammillary bodies store neurotransmitters important for memory processes.

The hippocampi have hemispheric laterality functions akin to the language functions of the cortex. Verbal memory localizes to the left hippocampus and non-verbal memories such as memory for faces, geospatial organization, and musical memories localize to the right hippocampus.

The notion of a *single* anatomic locale for a memory is misleading; memories are formed with contributions from several brain regions, i.e., memories are distributed across brain regions with specific contributing roles. For example, the common memory or knowledge of the dangers connected with the smell of burning draws upon the memory link of the burning smell with fire that resides in olfactory heteromodal cortex while the affective association of fear with the smoky smell would derive from components of the limbic circuitry, most likely the amygdala. Damage to the "storage" areas can result in highly nuanced and subtle deficits or dissociations, e.g., déjà vu phenomena.

As noted above, explicit memory uses the limbic structures, primarily the hippocampal formation, medial temporal lobe and diencephalon. Implicit memories are stored in the host cortical regions for the specific function, e.g., visual memories in parieto-occipital regions and procedural memories in the motor cortex. These memories are distributed in both primary sensory and heteromodal areas.

3.3. The Symptoms of Amnesia

The hallmark of an amnestic disorder is the disruption of *anterograde* memory or the ability to learn and retain new information, and to form new memories. The impairment in new learning is not total: new information can be learned through *implicit* cognitive strategies such as conditioning or priming. These strategies are demonstrable experimentally but do little to mitigate the functional devastation caused by the impairment in explicit memory. Functioning in everyday life requires the ability to continually learn new information (i.e., form new memories) and as well the ability to consciously recall this information as needed. *Retrograde* amnesia is also usually present though it is less prominent and less disabling. It typically follows Ribot's

law with memory for recent events more affected than information learned long ago. The essential elements of all amnestic disorders are:

1. Anterograde amnesia, meaning the patient has severe deficits in learning new ideas, names, or episodes.
2. Retrograde amnesia is also present though to a lesser extent with a temporal gradation such that older memories are more preserved.
3. General cognition is largely intact.
4. Immediate memory, otherwise known as attention, working memory or registration is intact.
5. Procedural memory or the ability to learn new tasks or motor sequences (as opposed to new words or episodes) is largely intact.
6. The ability to learn implicitly is intact though of limited use.

In short, amnestic disorders are disturbances of new learning or short-term memory. Long-term memory is spared. It is explicit memory processes, i.e., memories learned and retrieved through conscious effort that are affected. Implicit memory processes can remain intact.

3.3.1. Anatomy and Symptomatology

The previous discussion of the anatomy of memory is useful in understanding the symptoms of amnestic disorders. New learning is impacted primarily because these are disorders that affect the hippocampi or diencephalon, the primary structures of new learning. Remote memories are largely intact because these memories are consolidated and protected within the lateral temporal lobe or other function-specific regions that remain undamaged in the conditions that cause amnestic disorders. Similarly, implicit memory skills remain intact as they utilize structures other than hippocampi and diencephalon; as such, the amnestic patient can still learn through priming, conditioning, and other implicit means though the utility of such learning, in the absence of an ability to consciously recall is limited.

3.3.1.1. Associated Symptoms

Confabulation is the production of false information in response to a question or stimulus. It is not lying in that the confabulator has no conscious intent to dissimulate and believes what he just said. For example, the amnestic patient with no recollection of where he lives when asked might respond to the effect of "oh I live around here in the neighborhood, not far.... in my own little place." He does not respond, "I don't know" because of a pressure or push to respond that defines confabulation. Some see this as more a failure of executive control than memory: the executive "censor" whose role is to inhibit unreasonable interpretations and responses is allowing "the first thing that popped into my head" to escape into discourse. Confabulation is more common in diencephalic amnesia (e.g., Korsakoff's) suggesting an associated involvement of frontal circuitry in this disorder. Similarly a change in personality that can involve apathy or agitation often is part of the amnestic syndrome and might again be attributable to involvement of these frontal networks.

Motor and sensory symptoms may not be present at all as in Transient Global Amnesia or they may be quite prominent as in the Wernicke–Korsakoff syndrome. In the acute presentation of Wernicke's encephalopathy there is striking opthalmoplegia and gait disturbance. Even after timely treatment with parenteral vitamins there can be residual extra-ocular abnormalities including lateral or even vertical nystagmus. The gait disturbance arising from peripheral neuropathy, muscle weakness, or cerebellar degeneration related to chronic alcoholism can also persist.

3.4. Amnestic Syndromes

3.4.1. Wernicke–Korsakoff Syndrome

Korsakoff (1853–1900), the prodigious Russian neuropsychiatrist, in his lifelong study of the repercussions of alcoholism, described a condition that comprised a polyneuritis and a cognitive disorder in which memory was significantly impaired. He attributed the disorder to an as-yet unidentified toxin (5). Carl Wernicke, the German neuropsychiatrist, was simultaneously describing a condition also seen in chronic alcoholics that presented acutely with opthalmoplegia, gait ataxia, and confusion. He attributed the condition to inflammatory or cerebrovascular processes. Both of these disorders were quickly incorporated into the clinical lexicon and widely recognized in practice (6). However, it was not until the 1930s that it was appreciated that the disorders were similar and that both were attributable to a vitamin deficiency (Vitamin B1 or thiamine) not unique to alcoholics.

Maurice Victor and Raymond Adams subsequently described diencepalic degeneration as the hallmark neuropathological feature (7, 8). They advocated a unitary term, Wernicke–Korsakoff syndrome, which remains in widespread use though with variations. Wernicke's Encephalopathy or Wernicke's Dementia is often used to refer to the acute presentation for the vitamin deficiency and Korsakoff's Dementia or Psychosis is used to refer to the chronic amnestic states that persist after the initial presentation. This amnesia as originally described by Korsakoff is the paradigmatic amnestic syndrome: "at times an almost pure form of acute amnesia where the recent memory is well preserved though the remote past is remembered quite well." Korsakoff's original papers also capture the variability within the syndrome with some patients presenting with greater or lesser degrees of dilapidation in other cognitive domains, as well as behavior and function.

3.4.2. Transient Global Amnesia (TGA)

TGA, first described in 1964, is characterized by a sudden inability to record new memories in previously non-demented patient (9). There are no associated motor or sensory deficits, no impairment in any other cognitive domain, and the sensorium is clear. A frequent presenting feature is repetitive questioning regarding geographic or contextual orientation (e.g., where are we? Where are we going?). It typically occurs in middle age or later and seems to affect men and women equally. The episode can last minutes to hours after which the ability to form new memories gradually returns, the only residual effect is a persistent amnesia for the actual episode and events that occurred during the period of anterograde amnesia. TGA tends not to recur. The etiology is unknown though some advance a vascular spasm hypothesis akin to migraines as a mechanism (10). Others have proposed cerebral venous insufficiency, seizures, and transient arterial ischemia as possible etiologies though none of these occur regularly in studied patients with TGA and do not as yet adequately explain the symptomatic specificity of the syndrome (11, 12).

3.4.3. Mild Cognitive Impairment (MCI)

This is likely the most common type of amnestic syndrome. MCI is defined in most operational criteria by:

- A subjective deficit in memory, preferably corroborated by another informant.
- Objective deficits in performance on memory tests, compared with other people of similar age and educational background. The overall performance might still be within the established range of normal but should be below expectation for this patient considering his/her premorbid intelligence, level of education, or occupational achievement.
- Essentially normal judgment, perception, and reasoning skills.
- Largely normal activities of daily living.
- Absence of dementia.

The above definition refers to the "amnestic type" of MCI. There is also a "non-amnestic" MCI though the definition and predictive value of this entity is not as well established.

Ten to twenty percent of those over the age of 70 have mild cognitive impairment. Of those diagnosed with MCI, 10–15% will progress to an Alzheimer's disease diagnosis in each year following identification of MCI such that at 3 years post-diagnosis with MCI, half will have frank Alzheimer's. What emerges is that MCI can serve as a pre-Alzheimer's diagnosis, though it can be the precursor state for other dementias as well. In addition, there are patients who do not progress or even those who improve. MCI diagnostic criteria will collect a clinically heterogeneous population (13, 14).

3.4.4. Hysterical Amnesia

Amnesia can represent a hysterical response in a vulnerable patient similar to hysterical paralysis or hysterical epilepsy. The so-called dissociative or psychogenic amnesia involves difficulty recalling details or circumstances related to a particular event usually of a traumatic nature. For example, a patient who had been assaulted presented to an emergency room after the assault and provided a detailed accounting of the event. However, 2 days later she presented with no knowledge of the assault and over the next week she became amnestic to earlier traumatic life events and subsequently was unable to recall her address or the names of immediate family members. This sort of non-chronological and situation-specific amnesia is characteristic of hysterical amnesia.

In hysterical amnesia there may be an extensive retrograde amnesia extending over days, weeks, or even years though anterograde memory or new learning is intact. This contrasts sharply with the amnestic syndrome described above in which anterograde memory is densely impaired and retrograde memory follows Ribot's law with most recent memories more vulnerable to loss.

In typical amnesia there can be significant recovery of memory over time whereas in hysterical amnesia the deficits may worsen with time. Hysterical amnesia can include amnesia for person, something that is virtually never seen in the amnestic disorders and is seen in progressive dementia only at the terminal stage (15, 16).

3.5. Etiologies for Amnesia

There are numerous potential etiologies for the amnestic syndrome, listed in Table 3.1. These include head trauma, vitamin deficiencies, hypoxic conditions, cerebrovascular disorders, toxic exposures, specific infections, and the idiopathic transient global amnesia. What is common to all these provocative etiologies is the relatively focal involvement of the limbic or diencephalic circuitry that subserves new learning or "short-term memory."

3.5.1. Hypoxic Conditions

The hippocampi are exquisitely sensitive to oxygen deprivation. Hence any interference with the supply of oxygen to the brain can differentially impact the hippocampi and create the relatively narrow symptoms of the amnestic syndrome. Anoxic injury due to cardiac sudden death or shock can produce discrete infarction of the hippocampi even as the rest of the brain is salvaged with cardiopulmonary resuscitation. Carbon monoxide poisoning, as in failed suicide attempts interferes with the oxygen transport within the red blood cells and can selectively impact the limbic memory structures. Focal necrosis of the hippocampi can be seen at autopsy and at times on imaging.

"Pumphead" or post-perfusion syndrome, in which cardiac surgery patients develop abiding cognitive deficits after surgery involving mechanical perfusion has long been part of clinical lore. A landmark study in 2001 found that over 40% of patients in this series had a performance decline of 20% or more from pre-surgery testing (17). However, large retrospective studies of dementia patients have found they were no more likely to have had cardiac surgery previously than a non-demented control sample. If post-perfusion syndrome is a true phenomenon then it is a subtle change in cognition rather than a full dementia. It is not progressive, as the deficits are related to the insults associated with surgery, presumably micro-emboli, and further decline would not be expected (18, 19).

3.5.2. Infections

Herpes simplex encephalitis causes a focal hemorrhagic necrosis that usually localizes to the temporal and frontal lobes. It is caused by herpes simplex virus type 1 (HSV-1). There is a high mortality rate but survivors often display a focal amnestic disorder due to destruction of mesial temporal structures. General cognition is largely intact.

3.6. Evaluation

The evaluation of an amnestic patient often takes place in an emergency room or inpatient hospital ward as the deficits may be screaming for attention. The single most important aspect on initial evaluation is determining if the patient is presenting with an acute Wernicke's encephalopathy. Extra-ocular movements and gait must be assessed and there should be a low threshold

TABLE 3.1. Common etiologies for the Amnestic Syndrome.

Acute onset	Insidious onset
Transient global amnesia	Korsakoff's dementia/psychosis
Traumatic brain injury	Other vitamin deficiencies due to malabsorption, persistent vomiting, malnutrition
Wernicke's encephalopathy	Post-herpetic encephalopathy
Anoxic encephalopathy as seen post-cardiac or respiratory arrest; thrombotic or embolic events, carbon monoxide poisoning	Mild cognitive impairment (MCI)
Electroconvulsive therapy (ECT)	
Anesthesia	
"Pumphead syndrome"	
Alcohol or sedative–hypnotic intoxication	

for administering intravenous B vitamins: the potential to reverse severe deficits is present only at this early stage. Bedside examination can elucidate the disproportionate devastation of memory that characterizes the amnestic disorder. Casual conversation will appear normal as the patient has intact verbal skills and will often confabulate to fill in a reasonable context. Bedside cognitive testing, however, will quickly demonstrate the deficits. The patient will be wholly disoriented in the absence of a wall calendar, watch or newspaper at hand (though will retain the insight and ability to look over at the calendar or his watch). Asking the patient to register and recall a list of items or words will make manifest the deficits. The amnestic will be able to repeat back the list of words as long as he can keep them in working memory (e.g., by focusing on the words or repeating them to himself). However, after an intervening task such as serial 7 subtractions (which he will be able to do as general cognition and calculating skills are spared) the words will be lost without trace. No hints or cues will bring these words back as they have left no memory trace. Short-term memory or new learning has failed. Neuropsychological testing can further delineate the extent of the impairment in new learning and the relative preservation of other cognitive domains.

Neuroimaging is often unremarkable in the amnestic disorders, in large part because the structures involved, the hippocampi and diencephalon are small and don't always show damage on conventional scanning methods.

The main differential in amnestic presentations is delirium and dementia. Delirium is the great mimicker of psychiatric symptoms and delirious patients can present with disorientation in all spheres and profound inability to retain new knowledge.

Delirium is defined by a disturbance in attention and consciousness, both of which are entirely intact in the amnestic patient. In the delirious patient the EEG reflects this disturbance in sensorium with a diffusely slow background rhythm. In amnestic disorders, the EEG is unremarkable.

Dementias also present with clear consciousness and significant impairment in new learning. Dementias, however, by definition, involve other cognitive domains such as language, calculation, or comportment.

3.7. Treatment

The treatment of amnestic disorders requires careful determination of the etiology and then treatment for that condition. Amnestic disorders can present emergently such as in Wernicke's encephalopathy with a narrow timeframe of hours during which intravenous provision of thiamine might reverse the symptoms and prevent enduring amnesia. Transient Global Amnesia resolves spontaneously though the typical middle aged patients presenting with this sudden onset memory impairment need to be evaluated emergently for stroke, seizures, or a space-occupying brain mass. Hysterical amnesia should be treated, as other hysterical phenomena with the use of suggestion to promote a belief that that memory will recover quickly in its entirety. Hypnosis or controlled narcosis such as that obtained with amobarbital can be used to provide post-hypnotic suggestion that memories will return.

Other amnestic disorders present after the fact, i.e., after the damage to brain tissue is irrevocable as in anoxic brain damage or post-herpetic encephalopathy. In these cases the treatment is nonspecific and aimed at ameliorating symptoms. Case management becomes the more essential intervention. These patients will likely require a guardian of person and effects, supervised housing and a sheltered work environment if they are to work at all.

Nonspecific treatments that can be used for chronic amnestic disorders include cholinesterase inhibitors for enhancement of memory; antipsychotic or anticonvulsant medication for intrusive disinhibition or agitation; and psychostimulants for disabling apathy or abulia. All of these symptomatic interventions are off-label and have minimal quality evidence to support or discourage their use. Cognitive rehabilitation or remediation and memory enhancement programs have theoretical utility here as amnestics can learn through implicit means such as conditioning and priming and still have access to procedural and more remote ("overlearned") semantic memories. However, all these approaches are confounded by the impairment in conscious recall, i.e., even if the amnestic can learn associative mnemonics, if he cannot learn that he knows these mnemonics, they will never be called in to play in a given situation where they may have been useful. Similarly, having access to a rich base of procedural skills such as master carpentry is not helpful if the patient cannot recall where the building materials are stored or if he was to build a house or a rocking chair. A job coach can act as an external conscious memory though this is rarely feasible for extended periods of time.

Attempts to supplement a failed conscious recollection through the use of technological supports such as smart phones, electronic organizers, or personal robotics are again limited by the patient's inability to remember to take the phone with him or inability to learn even the rudimentary operating procedures for the technical innovation.

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4
Bipolar Illness

William Coryell, M.D. and Paula J. Clayton, M.D.

Abstract This chapter records the historical significance of the disorder, mania, a symptom complex that has been recognized since antiquity. It shows the development of the concept of bipolarity and the more recent broadening of the concept. This is followed by etiologic considerations, with emphasis on the genetic components, and its epidemiology, risk factors, clinical picture, course, complications, differential diagnosis, and treatment. Updates in this revision apply to all areas subsequent to the history of the concept. They are particularly extensive in the areas of genetic underpinnings, the onset and course of the illness, those features with prognostic value and the various treatment options. Given the considerable accumulation of new findings since the first edition of this volume there is also a new emphasis on meta-analyses to better allow for tentative conclusions.

Keywords Bipolar I · Bipolar II · Mania · Depression · Hypomania · Rapid cycling · SAD · Secondary mania · Mood stabilizer · Course · Suicide

4.1. History

Numerous terms, usually dichotomous, have been used to classify mood disorders. The separation into unipolar disorder and bipolar mood disorders rests on extensively described genetic and clinical differences and has become the most fundamental and widely used of them. Unipolar mood disorder refers to patients who have depression only. Bipolar mood disorder designates patients who have episodes of mania or hypomania. Hypomania without a history of depressive episodes is not considered a diagnosable disorder (1).

Hippocrates is credited with introducing psychiatric diagnoses into medical nomenclature. Two of the six diagnoses that he proposed were mania, derived from a Greek word "to be mad," and melancholia, from "black bile." In his classification, mania referred to acute mental disorders without fever, and melancholia referred to a wide variety of chronic mental illnesses. In the first century AD, Aretaeus noted that depression and excitement often alternated in the same person and therefore might represent different aspects of the same illness. Although it is difficult to tell from the classification systems how pervasive this idea of cycling became in the centuries thereafter, the term mania remained prominent in all. For hundreds of years the diagnosis of mania has been used primarily for an illness with an acute onset and with a mood of merriment, rage or fury (2).

In 1686, Bonet used the term maniaco-melancholicus to characterize such patients. In the 1850s, Falret adopted the term circular insanity, and Baillarger used that of double-form insanity for similar patients (3). In 1874, Kahlbaum (4) referred to patients with cyclothymia. Kraepelin (5) drew on and synthesized the various approaches to nosology bequeathed to him from the preceding centuries. Beginning in 1883, he published nine editions of his textbook on psychiatry, and it was he who separated dementia praecox from manic-depressive illness using clinical descriptions and the natural history of the illnesses.

W. Coryell, M.D. (✉)
George Winokur Professor of Psychiatry, Department of Psychiatry, University of Iowa Carver College of Medicine, Iowa City, IA, USA
e-mail: william-coryell@uiowa.edu

P.J. Clayton, M.D.
Professor Emerita, University of Minnesota School of Medicine and University of New Mexico School of Medicine, Pasadena, CA, USA
e-mail: pjcpsych@aol.com

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If we could assume that names are given to illnesses in an attempt to organize clinical observations, then it must be said, from the long history of the term mania, that the particular symptom cluster and course of mania has been apparent to clinicians throughout history.

Lange (6) may have first suggested the separation of unipolar from bipolar illness. Pederson et al. (7) noted "periodical depression has no manic phases and differs from manic-depressive psychoses with regard to heredity as well as distribution of somatic types and prognosis." They added that manic-depressive patients were more likely chronic and disabled in contradistinction to periodic depressives, who were more likely to be discharged and recovered. Leonhard (8), Perris (9), and Angst (10) solidified this point of view and the first American researchers to place emphasis on this distinction were Winokur and Clayton (11).

Although bipolar illness was separated from unipolar illness on the basis of differences in age of onset, course, family history, and response to treatment, this separation may not, in the end, prove entirely valid. More recently some data has accumulated that suggest, as Kraepelin (5) did, that the two illnesses may be different forms of the same disorder, with bipolar illness being a more severe, earlier-onset form than recurrent major depressive disorder. This unitary approach has been gaining momentum in the last 10 years and is best exemplified by Cassano et al. (12) and Akiskal and Benazzi (13).

4.2. Definition

Manic-depressive disease, or manic-depressive illness, is the old term for bipolar disorders as described in the Diagnostic and Statistical Manual of Mental Disorders (DSM 5). Bipolar I disorder requires a history of manic episodes and bipolar II disorder requires both episodes of depression and hypomania in the absence of any episode of mania. Cyclothymic disorder is characterized by at least 2 years of numerous episodes of hypomanic and depressive symptoms. Other Specified Bipolar and Related Disorders encompass presentations which feature symptoms that are characteristic of bipolar disorder but which do not meet the full criteria.

Bipolar I disorder may manifest with manic or depressed phases and either type may include an admixture of the other syndrome. If three symptoms of mania or major depression coexist with the full alternate syndrome for most days of the episode, it is said to have mixed features. The coexistence of full syndromes of both major depression and mania is considered to be a manic episode with depressive features.

For a diagnosis of a manic episode, DSM-5 requires presence of an irritable or elevated mood as well as increased energy and three or more of seven symptoms that last for 1 week. The symptoms cause social impairment and the episode should not be due to an abuse of a drug or a medical condition or treatment.

Specifiers can be used to identify patients with mood-congruent or mood-incongruent psychotic features. This distinction hinges on whether the content of delusions or hallucinations is, or is not, consistent with typical manic themes. If mood-congruent and mood-incongruent features coexist, the episode is specified as mood-incongruent.

Major depressive or manic episodes that begin during pregnancy or within 4 weeks following delivery are specified as having a peripartum onset. If three or more of 12 listed catatonic features dominates a major depressive or manic episode, that episode is considered catatonic.

Bipolar II disorder requires a history of at least one hypomanic episode and of one or more major depressive episodes. The criteria for a hypomanic episode resemble those for a manic episode except that the minimum duration is 4 days and symptoms must not include psychotic features and do not necessitate hospitalization or result in marked impairment.

4.3. Etiology

Genetic factors play a significant role in the etiology of bipolar affective disorder. No other data concerning etiology are as strong as those in the genetic area, and knowledge of family history appears to have practical value. The development of the genome map and of DNA probes for linkage markers led investigators to anticipate the identification of linkages to specific chromosomal markers. To date, however, only a few reproducible risk alleles have been detected. It may be, instead of using categories to divide individuals as affected, unknown and unaffected, it will be more informative to separate individuals by dimensions.

In addition to the genetic factors, studies have also investigated possible etiological roles for biochemical, neuroendocrine, neurophysiologic, and chronobiological abnormalities. Evidence that particular abnormalities are specific to bipolar illness over MDD has been scant, however. Besides the problem of always including some not-yet-identified bipolar patients in unipolar studies (at least 25–33%, up to 50%) one must always consider if the abnormalities described in any particular report occurred during a unipolar or bipolar depression, during a manic phase, pure or mixed, or in a well state, and under what conditions (i.e., on, or recently on, medications).

4.3.1. Genetics

There is no doubt that bipolar disorder is familial; that is, it runs in families, with close relatives being more likely to be affected than unrelated subjects. Three types of studies show the extent to which this is true: (1) family studies, (2) adoption studies, and (3) twin studies.

4.3.1.1. Family Studies

Family studies were originally anecdotal. Falret in 1854 interviewed the parents of patients with circular insanity and obtained compelling evidence as to the hereditary disposition in the illness (3). He concluded that circular insanity was very heritable, but could not decide whether it was more heritable than any other type of mental illness, although he was inclined to think so.

Many decades later Perris (9), Angst (10), and Winokur and Clayton (11) confirmed the heritability of bipolar illness with a series of family studies. Many others have followed and a review of those that included normal control groups estimated that the first-degree relatives of bipolar patients have a sevenfold increase in risk for bipolar illness over that of control subjects (14).

In addition to providing some support for the role of genes in the etiology of bipolar disorder, the results of family studies also speak to the validity of distinctions between bipolar and unipolar disorder and between bipolar I and bipolar II disorders. Their relevance to boundaries between bipolar I disorder and schizoaffective disorder, bipolar type, is covered in the chapter on schizoaffective disorder.

For the first of these distinctions, nearly all comparisons between the relatives of bipolar patients and those of unipolar patients have found the former to have substantially higher rates of bipolar illness. Some have also found more unipolar illness among the relatives of bipolar probands than among controls but this may be accounted for, in large part, by the substantial proportion of seemingly unipolar patients that eventually develop manic episodes. In fact, a family history of mania is among the most reproducible of the features that predict the development of mania among seemingly unipolar patients (15).

Regarding the distinction between bipolar I and bipolar II conditions, relevant studies appeared later and are fewer in number. The largest of these used data from the NIMH Collaborative Depression Study (CDS) (16). In a comparison of non-bipolar, bipolar II, and bipolar I probands grouped according to Research Diagnostic Criteria (RDC) (17), bipolar II disorder was most often diagnosed in the relatives of bipolar II probands and bipolar I disorder in the relatives of bipolar I probands (18). Other studies have observed a similar pattern (19).

More recent support for the separation of bipolar I and bipolar II conditions derives from an analysis of risk factors for diagnostic stability over a lengthy observation period (15). Probands who began follow-up with a diagnosis of non-bipolar disorder were more likely to switch to bipolar II disorder if their interviewed relatives had bipolar II disorder. Those who switched to bipolar I disorder were more likely to have had relatives with bipolar I disorder.

The diagnostic reliability of bipolar II disorder is problematic for several reasons. First, because patients rarely seek help for a hypomanic episode, clinicians usually diagnose on the basis of episodes that occurred in the sometimes distant past. Second, because hypomania, by definition, does not result in serious impairment and, in contrast to most mental disorders, need not involve impairment at all, such features as increased mood and energy may shade imperceptibly into correlates of normal mood fluctuations.

The CDS findings of Rice et al. (20) are pertinent to this problem. First-degree relatives of probands with MDD or bipolar disorder were reinterviewed blindly after a 6-year interval. A history of hypomania obtained at the first interview was recalled in the second interview in only 1 of 10 cases. Of the seven given a diagnosis of bipolar II disorder in one but not the other interview, all were related to probands who had a bipolar disorder. This suggests that if at least one of repeated screenings for past hypomania is positive, then the true diagnosis is most likely to be bipolar II disorder, even if some of those screenings were negative.

4.3.1.2. Adoption Studies

In contrast to family studies, adoption studies offer a means to separate familial transmission attributable to being raised by a parent with bipolar disorder from that due to being genetically related. Adoption studies are understandably difficult to accomplish and only two exist for bipolar disorder. One of these found that the adopted-away offspring of bipolar biological parents were four times more likely to have bipolar disorder than were adopted-away offspring of parents without bipolar disorder (21). Another found a twofold difference (22).

4.3.1.3. Twin Studies

Comparisons of monozygotic and dizygotic twins with and without bipolar disorder are another way to separate nature and nurture. The systematic review of six of these yielded median concordance rates of 39 and 5% for monozygotic and dizygotic

twin pairs, respectively (23). The heritability of bipolar I disorder is approximately 80% (24, 25), more than twice the 35% for unipolar major depression as derived from a weighted mean across seven studies (26). The heritabilities of bipolar II disorder and cyclothymia have been estimated at 58% and 68%, respectively.

4.3.1.4. Genetic Studies

Many linkage studies of bipolar disorder have sought to identify rare gene variants that carry high disease risk. The lack of clearly replicable findings has led to the conclusion that very few cases of bipolar disorder result from such genes. Rapid advances in the efficacy of genome mapping have made possible studies of unrelated subjects in order to detect population-level associations between disease and genes of smaller effect. Further progress in the relevant technology then allowed genome-wide association studies (27), an approach that has had some success. Currently, a small number of polymorphisms have shown associations that are strong and replicable (28).

Perhaps the most notable of these is CACNA1C (29). This gene encodes major L-type alpha subunits in the brain and is thus of particular interest given the apparent efficacy of L-type calcium channel blockers in mood disorders (30). However, this and other polymorphisms within the calcium channel subunit have also been associated with MDD and schizophrenia (31). Such findings have revived controversies over the Kraepelinian distinction between schizophrenia and mood disorders and have supported a greater emphasis on the study of spectrum variables rather than diagnostic categories (32).

4.3.2. Biochemical and Neuroendocrine Parameters

The depressant effect of reserpine when given for hypertension, and the antidepressant effects of a monoamine oxidase inhibitor when given for tuberculosis, led to the development of the biogenic amine hypothesis for the etiology of depression. The classic amine hypothesis held that depressive illness arises from a functional deficit of either norepinephrine or serotonin at critical synapses in the central nervous system. Conversely, an excess of such amines is associated with mania. It is evident that the third biogenic amine, dopamine, is also important and that other neurotransmitters or neuromodulators, such as those of the cholinergic, GABAergic, and endorphin systems, play roles in bipolar disorder. Janowsky et al. (33) suggested that an affective state may represent a balance between central cholinergic and adrenergic neurotransmitters and that depression may be a disorder of cholinergic predominance and mania, the opposite. In keeping with this, pilocarpine has been shown to rapidly decrease manic symptoms (34). More recently glutamatergic modulators have attracted particular interest in the search for additional new stabilizers (35).

Early observations of the affective state of patients with excesses or deficiencies of corticosteroids (Cushing's syndrome and Addison's disease) led to the measurement of corticosteroids in the plasma and urine of patients with depression. Some depressed patients had elevated levels of corticosteroids that returned to normal with recovery (36). Capitalizing on an endocrine challenge test for the diagnosis of Cushing's disease, Carroll et al. (37) began to systematically evaluate the dexamethasone suppression test (DST) in depressed patients. They reported that 67% of depressed melancholic inpatients and outpatients given 1 mg of dexamethasone at 11:00 p.m. failed to suppress cortisol at 8:00 a.m., 4:00 p.m., or 11:00 p.m. the next day (37).

The prospect of a long awaited diagnostic laboratory test in psychiatry together with the pathophysiologic implications of the findings and the ease with which the DST could be conducted, resulted in a profusion of studies. A recent review of published comparisons between samples with depressive disorders and comparison samples included those from 361 studies (38). The preponderance of findings indicated substantially higher rates of HPA axis hyperactivity in the depressed groups with an effect size of $d = 0.70$ for results of the DST. Effect sizes were higher in groups with older mean ages or with greater overall severity and were therefore larger in groups comprised of inpatients or of patients with melancholic or psychotic depression. Despite some findings to the contrary, most studies of bipolar disorder found HPA hyperactivity to be more likely in depressed and mixed manic phases than in purely manic phases.

4.3.3. Chronobiology

Numerous lines of evidence link bipolar disorder to disturbances in biological circadian rhythms. These include observations of phase advances in patients with bipolar disorder (39), the therapeutic benefits of induced phase advances (40), of sleep deprivation (41), and of morning light exposure, whether administered intentionally (42) or not (43). Also relevant is the seasonality that many with bipolar disorder experience (44) and the tendency for travel across time zones to provoke mania or depression, depending on the direction of travel (45, 46). Accordingly, refinements of therapeutic interventions that affect these rhythms have evolved to include serial sleep deprivation (47) and sleep deprivation combined with light therapy (48), lithium (49, 50), or antidepressants (51–53).

4.3.4. Brain Imaging

Numerous structural imaging studies exist and have generated highly variable results, perhaps because typical sample sizes have not been large enough for the number of regions tested (54). Among the more consistent observations are that, in comparisons to well controls, bipolar patients have larger lateral ventricles and smaller cross-sectional areas of the corpus callosum. Hyperintensities, particularly those that are manifest in deep white matter, are substantially more prevalent in patients with bipolar disorder than in well controls or in subjects with unipolar disorder (54). Relative to those with MDD, individuals with bipolar disorder have smaller corpus callosum cross-sectional areas and larger hippocampal volumes (55). Because bipolar patients taking lithium have larger hippocampal grey matter volumes than do those taking other mood stabilizers (56), the much greater use of lithium in bipolar disorder than in unipolar disorders may account for the observed differences between them in hippocampal volumes.

Functional neuroimaging studies have also been numerous and have generated a variety of findings. In a recent meta-analysis of functional neuroimaging in bipolar disorder that identified 55 studies (57), subjects with bipolar disorder had limbic hyperactivity and frontal hypoactivity in comparison to control subjects. This pattern was present in euthymic and depressed states but was most prominent in manic states.

4.3.5. Secondary Mania

Krauthammer and Klerman (58) thoroughly reviewed the literature on secondary mania, and required specific criteria for mania. The majority of reported causes were neurologic conditions such as neoplasm, epilepsy, head injury, cerebrovascular lesions, drugs, metabolic or endocrine disturbances, infections, or other systemic conditions.

Reviews of differences between organic and non-organic mania (59–61) have shown that patients with induced mania are frequently older at illness onset, their mood is more often irritable than manic, and they are less frequently psychotic. Their family histories are also more frequently negative, and they respond preferentially to anticonvulsants.

Mania may develop after a closed head injury (62–64). In a comparison of a large number of patients with bipolar disorder to well controls, those with a history of head injury were clearly overrepresented in the former (65). This relationship only existed for those whose injuries had occurred within 5 years of their admission for mania and was most prominent for admissions that had occurred within 1 year.

The relationship between stroke and the onset of mood disorders has also been well studied (66, 67). In a meta-analysis of 49 reports, the typical patient that developed mania following a stroke was a male with a right-sided infarction and without a personal or family history of psychiatric disorder (68).

4.4. Epidemiology

Because of the inclusion of BP II, estimates of the prevalence of bipolar disorder have increased since those reported by Boyd and Weissman (69) and by the ECA studies (70). Lifetime prevalence rates for DSM IV bipolar disorders (I and II) from the National Comorbidity Survey Replication were 3.9% (71). Rates varied inversely by age. Although prevalence rates for schizophrenia were not measured in these studies, bipolar illness is clearly the more common illness. Moreover, the cited rates did not include all of the cases of MDD that would later switch to bipolar disorder. Some authors contend that Major Depression and Bipolar Disorders may be nearer to equal in prevalence, mainly because of the BP II individuals embedded in the MDD group (72, 73). In most studies the distribution of males to females is balanced in BP I but is 2:1 female to male in BP II.

There are no racial differences in the incidence or prevalence of this illness. Evidence exists that both Hispanics and blacks with bipolar affective disorder are more likely to be misdiagnosed as having schizophrenia (74–76). In the ECA study (70), there were no differences in the lifetime prevalence of mania by race and mania was equally prevalent in urban or rural residents.

A relationship between bipolar disorder and creativity has long been appreciated (77). Studies of probands and relatives in the past several decades have likewise associated bipolar disorder with high educational and occupational achievement, but this appears to be true of the relatives of bipolar probands, rather than the probands themselves (78–80). The advantage in bipolar family members was particularly strong in the relatives who themselves had bipolar disorder, however. This suggests that, though the diathesis toward bipolar illness carries with it traits that promote higher achievement, the disability associated with those cases of bipolar disorder that necessitate treatment at tertiary care centers may overwhelm this advantage.

4.5. Diagnostic Stability

A recent review of follow-up studies that used structured interview at baseline showed a median conversion rate to bipolar I or bipolar II diagnoses of 15% (15). Follow-up studies that derived baseline diagnoses of MDD from chart review often reported considerably higher conversion rates than did those based on structured diagnostic interviews. This illustrates the frequent failure to appreciate past episodes of mania or hypomania that occurs in typical clinical settings. In the study that combined a high-surveillance intensity with a particularly lengthy follow-up of up to 31 years, the conversion rate was 1 in 5 (19.6%). For switches specifically to bipolar II disorder and to bipolar I disorder, rates were 12.2% and 7.5%, respectively (15). Patients with an early age of onset, with psychotic features, or with a family history of bipolar disorder have higher rates of switching (15, 81). Any admixture of manic symptoms with a depressive syndrome, particularly those of decreased need for sleep or increases in energy or activity, substantially raises the risk of an eventual bipolar diagnosis (15).

It should also be remembered that individuals who appear to have bipolar disorder are at risk for an eventual diagnosis of schizophrenia. In a carefully executed study of diagnostic stability over 10 years, Bromet et al. (82) found that a change in diagnosis of bipolar disorder to schizophrenia (14/95 = 14.7%) was more than three times more likely than a diagnostic change in the opposite direction (5/126 = 4.0%, $p < 0.005$).

4.6. Course

Though numerous reports have described tendencies for adverse life events to precede both manic and depressive episodes (83), most that have taken care to focus only on those adverse events that were likely to be independent of symptoms have found adverse events to be no more common before than after manic episodes (84). On the other hand, life events that disrupt social rhythms, particularly those resulting in sleep loss, do appear to trigger manic episodes (85, 86). This observation has led to efforts to stabilize social rhythms as a part of the long-term management of bipolar disorders (87).

Parturition is clearly a trigger. All studies have confirmed the postpartum period as a risk period for mania in known bipolar patients (88–90), and in patients with serious previous depression (81). Women who experience post-partum episodes are likely to develop them again following one or more subsequent deliveries.

Numerous studies have indicated that, in the teenage years, bipolar illness can be seen as schizophrenia, antisocial personality, or borderline personality disorder. Akiskal (81) indicated that the clinical presentation of adolescents with bipolar disorders are, in decreasing frequency, psychosis, alcohol and drug problems, moodiness, suicidal ideation or attempt, academic failure, philosophic brooding, obsessional brooding, somatic complaints, school phobia, "hyperactivity," stupor, and flagrant antisocial behavior.

The literature on late-onset (more than 50 years of age) bipolar illness is confusing because some of the patients discussed had episodes of depression before the age of 50 but did not become manic until after age 50. A study of manic episodes in older people indicated that a mean of 10 years had elapsed between the first depressive episode and the first manic episode (91). Late onsets should trigger a search for an underlying medical condition but there are onsets after 50 that are not associated with organic pathology (92–95). Since this age group is enlarging we should see more.

Periodicity of this illness exists for some patients, with fall/winter depression and spring/summer mania being most frequently described. Sayer et al. (96) confirmed in the southern hemisphere what had been reported in the northern hemisphere (97), that hospital admissions for mania have a spring/summer peak. A lengthy study of week-to-week mood ratings similarly found a peak for depressive symptoms in winter, but also a peak for hypomanic symptoms near the fall equinox (44).

Such observations have led to the concept of seasonal affective disorder (SAD) (98, 99), and many with this condition have bipolar disorder. Indeed, a community study concluded that bipolar patients experience greater seasonality than those with depression or healthy controls (100). The recognition of such patterns may be important for the management of certain patients.

4.7. Clinical Picture

4.7.1. Onset

More than one-third of patients first develop symptoms consistent with bipolar disorder in the teenage years (88, 101). Although there are conflicting reports (102), most researchers agree that the majority of patients, particularly women, begin with depressive episodes (103–106). Bipolar disorder most often starts with an episode of pure depression. Angst (103) reported that the ratio of depression to mania in the first episode was 3:1 for women and 3:2 for men.

It is well established that the mean age of onset for bipolar disorder is earlier than that for unipolar disorder. Moreover, many age-of-onset admixture analyses have been done to refine groups for genetics studies and most have identified three groups.

Early, middle, and late onset groups usually fall in the ranges of 20 or less, 21–29, and 30 or greater, respectively (101). An early age of onset is, according to substantial evidence, indicative of poorer outcomes. Such patients have longer index episodes (107), more depressive morbidity over time (102, 108, 109), a higher likelihood of psychotic features, lesser responses to treatment (110), and a greater likelihood of rapid cycling (111–113). They also make more suicide attempts (102, 111–113) and are more likely to abuse substances (114). Aging itself, when tracked within subjects, seems to bring more time in depressive episodes but not more manic or hypomanic morbidity (115).

The type of initial phase with cycling episodes also has prognostic value. In comparison with patients who began with a depressive phase, those with mania as their first phase tend to show better responses to lithium (116–120) and to have shorter episodes generally (121).

4.7.2. Symptoms

Mania can begin suddenly with the development of a full-blown syndrome over hours, or it may appear more gradually, and develop over days. It seldom takes weeks to develop. A history of a change in the patient's behavior is usual although, unless the onset is sudden, close relatives may miss the first indications. Early in the course of illness, mania can be preceded by life events, including bereavement, but later episodes do not appear to follow life events as often (122). There are no data to suggest that unipolar mania differs from the bipolar mania. Kraepelin (5) originally reported that 17% of his 900 manic-depressive patients were exclusively manic. In the Jorvi Bipolar Study (JoBS) only 4.4% of these recently diagnosed inpatients and outpatients reported having mania only (106). In the CDS, 14 (8.6%) of 163 bipolar I patients who had at least 15 years of follow-up gave a history of only manic episodes at their intake evaluation (123) but this number dwindled to 7 (4.3%) over the course of follow-up.

The picture can vary from an excited, talkative, loud, over-reactive, somewhat amusing individual to a completely disorganized, intrusive, and psychotic one. The mood is, by definition, elated, angry, or irritable. Patients often appear overly confident, bragging, self-aggrandizing, and happy but become irritable when their ideas are not enthusiastically endorsed. Frequently they become most angry at those who are closest to them, particularly their spouses. They interrupt conversations but dislike being interrupted themselves. They are distractible, and racing thoughts, pressured speech, circumstantiality, irrelevancies, and flight of ideas characterize their thoughts and language. Decreased need for sleep, an increase in sexual thoughts, and an increase in alcohol intake are all common in the manic patient. During the full-blown syndrome, there may be periods of depression lasting from minutes to hours. Grandiose ideas and delusions are common and are often the basis for the symptoms of excessive telephone calls, extravagances, and excessive writing. One or two themes usually predominate and may be religious, political, financial, sexual, or persecutory. Catatonic features during manic episodes have been well documented (124, 125).

All varieties of psychotic symptoms have been reported in the manic patient (126, 127). One of the better descriptions of this is the Carlson and Goodwin study on the evolution of manic episodes (128). They described patients admitted to research units at the NIMH, where, because of participation in various protocols, manic episodes were often allowed to evolve fully before treatment began. At the height of manic episodes, patients exhibited unusual psychomotor activities, incoherent thought processes, and delusions and hallucinations that were bizarre and idiosyncratic. They found symptoms of hyperactivity, extreme verbosity, pressured speech, grandiosity, irritability, euphoria, mood lability, hypersexuality, and flight of ideas. Seventy-five percent had delusions that were either of control or had sexual, persecutory, or religious themes; 75% exhibited assaultive or threatening behavior; 60% were intrusive; 55% had some delusions; 45% had regressive behavior (urinating or defecating inappropriately and exposing themselves); 40% had auditory and visual hallucinations; and 35% were confused. Confusion is, in fact, a well-documented symptom of acute mania. In one chart review, 58% of 31 manic patients were reported either to be disoriented or to have memory lapses (126). Kraepelin (5) used the term delirious mania for this condition.

Pope and Lipinski (129) emphasized that between 20 and 50% of well-validated bipolar patients have psychotic symptoms, including hallucinations, delusions, catatonia symptoms, and Schneiderian first-rank symptoms. The presence of formal thought disorder either during a manic episode, or more especially, at some time outside of a manic episode, is a predictor of persistent delusional thinking after 5 years of follow-up (130).

Andreasen (131–133) studied thought disorder in mania and found that, besides being over-inclusive, manic patients were tangential and had derailment, incoherence, and illogicality that was as prominent as it was in schizophrenic patients. Manic patients were more likely to have pressured speech, distractibility, and circumstantiality, while the schizophrenics more frequently had poverty of both speech and content of speech. Some have found that at follow-up, though it is in partial remission, many continue to have thought pathology (134, 135).

Many studies have compared bipolar depression to unipolar depression by symptoms. Differences have been inconsistent (136) but an excess in bipolar depression of psychomotor retardation (137, 138) and psychotic features have been among the most replicable (139–141). Other distinctions that have distinguished the depression of bipolar II patients from that of bipolar I patients include more anxiety (137, 142) and a greater likelihood of rapid cycling (143, 144) in the former.

4.7.3. Course

It should be remembered that nearly all descriptions of course in bipolar illness have used samples recruited from inpatient settings and that little is known of the typical outcome of bipolar I and bipolar II patients who might be sampled in outpatient settings. Individuals with relatively severe or refractory illnesses are more likely to be found in inpatient settings and, of course, such patients would be expected to follow on average a more malignant course. The body of follow-up studies nevertheless allows the use of a number of features in making useful prognostic estimates.

The most consistently reported difference in course between bipolar and unipolar disorders, other than in the likelihood of manic or hypomanic episodes, is the shorter time to relapse and shorter cycle lengths in the former (122, 145–149). Follow-up studies published over the past 50 years show single episode cases of bipolar disorder to be quite rare (1, 148–151).

Bipolar I and bipolar II disorders differ markedly in the likelihood of future manic episodes (152). In comparison to patients with bipolar I, those with bipolar II disorder experience more weeks with depressive symptoms, both above and below the threshold for a major depressive episode (153). This observation is in harmony with the tendency of bipolar II patients to exhibit higher levels of borderline, histrionic, and schizotypal traits (154).

Evolution in cycle length has been a topic of conflicting reports. A number have described a shortening of cycle length as episodes accumulate (148, 155) and this has spurred speculation that episodes themselves produce brain changes that result in an increased propensity to new episodes (the kindling hypothesis) (156). Nearly all of these studies were entirely, or at least largely, retrospective in design and therefore shaped by the tendency to remember more recent episodes and to forget those in the distant past. Other descriptions that were entirely prospective in their tracking of episodes have revealed no evidence that cycles decrease in length (121, 157, 158).

The presence of psychotic features, whether in depressive or manic phases, portends greater symptom morbidity and psychosocial impairment in the long term (159–161). Psychotic features that are mood-incongruent appear to predict even greater psychosocial impairment (162–164).

Anxiety symptoms during bipolar depressive phases comprise another feature with sustained prognostic import. It is not clear which types of anxiety symptoms are most important, but their presence in general is associated with a higher likelihood of switching (165, 166), shorter euthymic periods (160), poorer treatment response (163, 167), more suicide attempts (160), and a longer time to remission (168). A high level of anxiety appears to mark a type of depressive illness rather than to simply characterize a given episode. The degree of difference in morbidity over time between anxious and non-anxious individuals does not lessen over decades of follow-up (115).

Cycling within a given episode indicates a longer time to remission (169, 170), a greater likelihood of subsequent rapid cycling (143) and more morbidity in the ensuing years (121, 171). Cycling (121) and mixed episodes (172) also increase the likelihood of such episodes in the future. Those who tend to present with single phases of mania have, on average, much better long-term outcomes (173, 174).

Rapid cycling is the more extreme form of cycling and its poor prognostic implications are well appreciated (175–177). Some patients exhibit this pattern chronically but the majority with a prospectively observed onset of rapid cycling ceased to have rapid cycling within 1–2 years of its development (143, 175).

The reported frequency of mixed states varies with the number of symptoms of the other pole that are required to define it. Some reports combine mixed and cycling episodes, which elevates the percentage identified as having a mixed state (174, 178–181). In any event, those with mixed onsets are more likely to develop rapid cycling (182).

Patients with mixed mania also have poorer responses to acute treatment (178, 179) and worse outcomes on follow-up (161, 183, 184). Depressive episodes with mixed features last longer on average, feature more intense dysphoria and both carry a higher likelihood of suicidal thinking and behavior and feature dysphoria that is more intense (185, 186).

Two early studies (88, 187), with follow-ups averaging 2 years and 6 years, respectively found that nearly 30% in both never achieved full remission. Welner et al. (188) later reviewed a large number of studies of bipolar illness and indicated that chronicity, if defined as presence of symptoms, social decline, or both, occurred in at least one-third of the bipolar patients. Chronic mania, however, is uncommon.

An analysis of the weekly status of bipolar I and II patients, most of whom who were hospitalized at the beginning of a lengthy follow-up, showed that the average patient with bipolar I disorder was ill for 47% of weeks (189) while those with bipolar II disorder were in episodes for 54% of weeks (190, 191). Sub-syndromal residual symptoms are an important problem for bipolar patients (191). Disability resulting from both depressive and manic symptoms increase steadily with increases in symptom number (192) and relapse into a full syndrome is much more likely in the presence of even mild subthreshold symptoms (193).

There are several more favorable outcome studies. One was Petterson (194) who observed the clinical, social, and genetic aspects of 123 patients in Sweden for approximately 5 years. At the end of the study, a large number of patients showed more satisfactory work capacity and better social adaptation. This was a group treated by a single investigator. Similarly, Miller et al. (195) also reported that their carefully treated patients were asymptomatic 59% of the time in a 23.7 month follow-up. So perhaps with complete and vigorous treatment in a stable clinical setting, the course is more favorable.

4.7.4. Consequences

4.7.4.1. Psychosocial Impairment

Bipolar disorder may cost twice as much in lost productivity as major depression disorder (196). It is estimated that each US worker with bipolar disorder averaged 66 lost workdays in a year compared to 27 for major depression.

Some have indicated that the marriage of bipolar patients end in divorce more frequently than those of unipolar patients or appropriate controls (197). In the CDS, patients with bipolar disorders were twice as likely to be divorced as were unipolar patients (198). Bipolar patients who were married, however, were only half as likely as were married unipolar patients to rate the relationship with their spouse as poor or very poor. Well spouses may have a different view though. In one report, 53% of well spouses compared with 5% of the bipolar patients indicated that they would not have married the spouse, and 47% of the well spouses, compared with 5% of the patients, would not have had children had they known about the bipolar illness before making these decisions (199). Thus, the illness has an impact on marriage, job, child rearing, and all aspects of life (200).

4.7.4.2. Suicide

A review of 27 studies of bipolar disorder showed a median suicide rate of 0.4 per 100 person-years (201). The 13 reports that included standardized mortality ratios had a median value of 22, indicating that individuals with bipolar disorder have a 22-fold greater likelihood of eventual suicide than do age- and sex-matched individuals from the general population.

In a 40–44 year follow-up of patients hospitalized for a mood disorder, 10.2% of those with bipolar disorder died by suicide (202, 203). Even though it was the more seriously ill patients who got treatment, the suicide rate was much reduced in those who were treated compared to those who were not. Outpatients have lower suicide rates in most studies (194, 204, 205).

Bipolar patients die by suicide in the depressed phase of their illness. One of the first psychological autopsy studies showed that although the most frequent diagnosis was one of a mood disorder, no patient was manic at the time of the suicide (206).

Findings have been uneven regarding whether risks for completed suicide are higher for patients with bipolar disorder than for those with MDD. In many reports, and particularly in retrospective studies, bipolar patients were more likely to have made suicide attempts (137, 169, 207). In prospective studies bipolar patients appear to have the same risk factors for suicide attempts and completions, as do MDD patients (208).

4.7.4.3. Cardiovascular Morbidity and Mortality

There are also links between bipolar disorder and excess cardiovascular mortality (209, 210). The increase in risk appears to be higher in bipolar illness than in MDD (211–213) and may be especially strong when the illness is not treated (202, 214, 215). The few studies that have compared bipolar I and bipolar II groups found significantly higher risks for cardiovascular morbidity in the former (208). The cumulative time already spent in manic or hypomanic episodes appeared to drive this risk (216).

4.7.4.4. Other Morbidity

Bipolar illness is associated with increased risk for dementia (217) as is MDD. Some of this association can be attributed to mood symptoms that are a prodrome of dementia, but a number of reports have described robust associations with mood disorders with onsets that have preceded the onset of dementia by many years.

Most mental disorders increase risks for alcohol use disorders, but the risk is highest in bipolar I and bipolar II disorders (218), and, relative to the general population, is much greater for women than men (219). Alcoholism may develop before or after bipolar illness first appears, and this order has some prognostic significance. Bipolar disorder which develops after alcoholism is established has a later onset and entails less affective morbidity over time (220, 221) The outcome for the alcoholism is poorer, however (220). This suggests that, when the onset of either bipolar disorder or alcoholism is facilitated by the presence of the other disorder, the course of the illness with later onset may be less malignant. Ongoing alcoholism or substance abuse, however, appears to predispose to mixed bipolar episodes (222, 223).

Some researchers have concluded that, in remission, manics evaluate themselves in a positive way (199, 224, 225). Others have emphasized the achievement-oriented personality of the bipolar patients (226, 227) and still others have found that bipolar patients who are well or stabilized on lithium have personalities similar to those of controls (228, 229). Some have suggested rather that lithium mutes underlying cyclothymia and causes bipolar patients to test more like unipolar patients (230).

A more recent look at distinct temperaments in 98 bipolar I, 64 bipolar II, and 251 unipolar major depressive disorder patients found that bipolar I patients described themselves as near normal whereas bipolar II patients emerged as mood labile, energetic, and assertive yet sensitive and brooding (231). Bipolar I patients were low on neuroticism and bipolar II patients were high,

mostly because of their mood lability. Angst and Clayton (232) compared premorbid personality traits in young men who went on to develop bipolar illness with those who remained well, and found no differences. Unfortunately, the personality test did not measure obsessionality—the trait, as reported by Klein and Depue (233), that may be associated with risk for bipolar disorder in the offspring of bipolar probands.

Rates of comorbidity in general are probably higher in bipolar disorders than in any other prevalent DSM IV disorder and this certainly extends to the personality disorders. Bipolar II disorder is more likely to be accompanied by personality disorders than is bipolar I disorder. Many patients with bipolar illness have high levels of impulsivity, a trait that worsens during episodes but then appears to remain higher than those of normal controls, even between episodes (221, 234).

With regard to criminality, Petterson's (194) patients had fewer convictions than expected in comparison with the general population, a finding replicated in other studies. An interesting set of studies (235), however, indicates that symptoms of mania are more common in forensic settings than was generally thought. Among patients admitted to St. Elizabeth's Hospital in Washington, DC, 11 of the 13 attempted crimes against the presidents of the USA, so-called White House cases, were perpetrated by people diagnosed as having an affective disorder, and the majority of them were bipolar.

There is also an association between pathologic gambling and a bipolar diagnosis (236). Pathologic gamblers have high rates of comorbidity, especially with bipolar disorder (237). In a large family study, the relatives of pathological gamblers were more likely to have bipolar disorder than were the relatives of control probands. This remained true when the effect of bipolar illness in the proband was controlled (238).

4.8. Differential Diagnosis

As indicated, there are other disorders that share many features with bipolar disorder. The distinction between bipolar disorder and some of these disorders is particularly problematic.

4.8.1. Schizophrenia

Schizophrenia and mania are alike in many ways. The symptoms of a current episode can be similar in mania and schizophrenia. There is not one symptom that is pathognomonic for either, although the mood of merriment, elation, ecstasy, or even irritability is much more likely to occur in mania than in schizophrenia. A study of diagnostic criteria for mania indicated that the triad of symptoms—manic mood, rapid or pressured speech, and hyperactivity—is relatively specific for mania (239). Thus, the presence of this triad should heavily tilt a differential diagnosis toward mania. In patients partially treated with lithium or other anti-manic drugs, these symptoms may be muted, and the prominent symptoms may only be psychotic symptoms.

Mania, for the most part, should have a relatively sudden onset, with the only extended prodromal symptoms being a depressive syndrome, and should be characterized as a clear change from the person's premorbid self. Schizophrenia is usually more insidious in onset, but it, too, can begin with depression or anxiety. Again, the other indications of a manic syndrome, such as increases in activity and decreased need for sleep, previous episodes, an acute onset, and family history, should help to differentiate patients. Prominent delusional thinking or hallucinations may overshadow manic symptoms in an acutely psychotic individual. In these cases a careful questioning of family members may reveal that manic symptoms were apparent in the lead up to fulminant psychosis.

The course of the illnesses can be similar. At least one-third of bipolar patients have either social disabilities or symptoms that may be more than just low-grade depressive symptoms. Still, all studies show significantly better follow-up outcome in manic individuals than in schizophrenics. Both have high suicide rates, with 10–15% dying by suicide. An important difference in these two illnesses is the family history. Although both are hereditable, at least 50% of manic patients have some family history of an affective disorder (mania or depression). Studies of schizophrenics show a significant but less striking increase in schizophrenia in their families but no increase in affective disorder over the population prevalence.

4.8.2. Catatonic Schizophrenia

Patients who present with catatonic symptoms are more likely to have bipolar disorder than any other diagnosis. All patients in whom the diagnosis of catatonic schizophrenia is entertained should be evaluated carefully for depressive and manic symptoms in the period preceding the onset of catatonic symptoms, for previous episodes, and for family history. Some manics become mute when their thoughts go so fast that they cannot speak. The amytal interview may still be useful in uncovering depressive delusions, disjointed manic thoughts, or disorientation (organicity) (240).

4.8.3. Schizoaffective Disorder

As is discussed in the chapter on schizoaffective disorder, this term has been given many definitions and its boundaries have varied accordingly as has its prognostic position between mood disorders and schizophrenia. Probably the most important component of the criteria in DSM-IV and DSM-5 is the requirement that, at some point, psychotic features have been manifest for at least 2 weeks in the absence of a mood episode. Many clinicians disregard this when they assign a schizoaffective disorder diagnosis.

4.8.4. Organic Mental Disorders

Because at least one-third of manic patients have either disorientation or some memory deficits during an episode, it might be easy to think of mania as a toxic state. Although certain drugs can precipitate manic episodes, usually even these syndromes are treated with neuroleptics or lithium, or both. A first episode in an elderly patient can be quite problematic and it is most difficult in a catatonic stupor. Previous history and family history should be useful in confirming a diagnosis. In younger patients it is important not to be sidetracked by the confusion of mania and to delay treatment for a long time while completing extensive organic workups.

4.8.5. Personality Disorders (Antisocial, Borderline) and Alcohol and Drug Abuse

There are many presentations of bipolar disorder. In the teenage years, a change in behavior would be the key to distinguishing the manic from the typical sociopath. It is easy if the sociopathic behavior is manic—that is, stealing with some grandiose plan in mind—but less easy if it is typical of all adolescent antisocial acts. The same can be said of alcohol or drug problems, school phobia, and borderline personality diagnoses. Here again, this should be a clear change in behavior that could not have been expected or anticipated. Depressive symptoms or, less commonly, previous manic symptoms should be present if inquired about. These things, coupled with a family history of affective disorder, should help in making the proper diagnosis.

Bipolar disorder shares the trait of impulsivity in particular with borderline personality disorder. Many other features overlap as well, including rapid mood shifts, propensity to substance abuse, frequently unstable interpersonal relationships, periods of striking irritability, a high risk for suicide attempts, and an often chronic course with early onset. As a consequence many patients with borderline personality disorder are misdiagnosed as having bipolar disorder and treated accordingly (241, 242). The relationship between borderline personality disorder and bipolar disorder is controversial and some believe they exist on a continuum (243).

4.8.6. Attention Deficit Hyperactivity Disorder in Children and Adolescents

The debate over the comorbidity of bipolar disorder and attention deficit disorder continues (244). Children who meet criteria for bipolar disorder are very likely to do so for ADHD as well (245). The two disorders share the symptoms of irritable mood, accelerated speech, distractibility, and high energy level (246). Symptoms that are relatively specific to bipolar disorder are grandiosity, elation, decreased need for sleep, and hypersexuality (247). Individuals who are comorbid for those disorders are more likely to have anxiety and substance use disorder and to have a criminal history (248). Notably, family studies have shown either bipolar disorder or ADHD to raise the risk of having the other disorder in relatives (249, 250). This opens the possibility that their coexistence represents a subtype of bipolar disorder.

4.9. Treatment

4.9.1. Acute Mania and Mixed Episodes

Little psychosocial management can be accomplished with a patient in the manic state. The patient is talkative, both irritable and irritating, sexually aroused, confident, expansive, and completely lacking in insight or good judgment. Because of the uplifted mood, the patient feels no need of treatment and refuses with vehemence offers of assistance. Hospitalization is necessary and frequently entails commitment. The patient must be protected against the serious social and medical consequences of this state. Because of the manic patient's intrusiveness and potential for creating conflict, it is almost always possible to think of that person as being dangerous to himself or herself. If there are other illnesses, such as hypertension, that are controlled by medication, these get out of control as the manic individual neglects medications, creating another reason for hospitalization.

When manic patients are hospitalized, their excessive energy is easy to handle if they are given space to roam and are not confined to a locked room. This does not mean that they can be on an unlocked unit, since they are capable of excessive spending even while in the hospital. Manic patients are also intrusive and speak in an uncensored way, so they can provoke arguments anywhere, including the hospital. In addition, enormous bills and bad feelings can result if telephone use is not restricted. The relatives, who are worn down and exasperated by the manic patient's behavior and relieved to know that he or she is being protected in the hospital, also often welcome hospitalization. The patient may also be super alert such that they hear and overinterpret everything they see and hear. It is best to maintain them in an environment with as little stimulation as possible; groups, occupational therapy, and television should be minimized until the illness is remitting.

In treating manic patients, physicians should always remember that certain interpersonal traits are part of the manic illness. Janowsky et al. (251, 252) outlined a series of interpersonal behaviors that they had originally thought were part of the manic's premorbid personality but that were later discovered to be symptoms of the manic episode. In addition to the classic manic symptoms of hyperactivity, push of speech, flight of ideas, irritability, distractibility, poor judgment, and increased social contact, they found that manic behavior included such things as the testing of limits, flattery, shifting responsibility for their actions to others, exploiting other's soft spots, dividing the staff, and provoking anger. These traits may lead to marked interpersonal, marital, and ward conflict. Therefore, in treating the manic patient, one must take into consideration these symptoms and behaviors and respond to them as if they were part of the illness. Setting limits in an unambivalent, firm, arbitrary way best does this.

The efficacy of lithium for acute mania is well accepted. With this in mind, the following choices are available, although the order may be debatable and may depend on the severity of the presenting symptoms: (1) lithium, (2) atypical antipsychotics or older antipsychotics (3) anticonvulsants such as valproate or carbamazepine alone or in combination with lithium, or (4) electroconvulsive therapy (ECT). Early studies comparing lithium with chlorpromazine or lithium, chlorpromazine, and haloperidol indicated that lithium was superior to the others in terms of earlier discharge. These studies, however, indicated that chlorpromazine, haloperidol, and other such neuroleptics control the hyperactivity/excitement of the acutely manic patient more quickly than does lithium. Some maintained that, clinically, the end result was superior with lithium alone, whereas others felt that haloperidol alone was sufficient for the acute illness. Because there have been some reports that the combination of haloperidol and lithium can produce adverse side effects (253–255), and because bipolar illness may increase risks for tardive dyskinesia (256–258), the newer second generation of antipsychotics, such as olanzapine, risperidone, quetiapine, ziprasidone, and aripiperazole, may be preferable for the treatment of acute mania.

Before beginning treatment with lithium, the patient's evaluation should include a physical examination, tests for thyroid and renal function (blood urea nitrogen and creatinine), a white blood cell count, and electrocardiography. Other medications should be recorded, particularly the use of diuretics. While the proper dose is being determined inpatients should be monitored daily for symptoms of toxicity, such as tremor, nausea, vomiting, diarrhea, and confusion. In general, if the dose is raised gradually, toxicity can be avoided. Skin rash, usually acneiform, is another potential problem.

The usual starting dose of lithium in acute mania is 300 mg three times a day, which is gradually raised until a blood level of 1.0–1.2 mEq/L is achieved. Lithium's half-life requires an unchanging dose for 5 days before measurement of steady state concentrations. Changes made on the basis of shorter intervals may overestimate doses and result in toxicity. Lower starting dose and smaller dose increments are appropriate for those over 50 years old (259). Once the patient has shown the ability to tolerate the lithium, the regimen should be switched to a single evening dose. That may be better for the kidneys. Improvement typically occurs in 8–10 days.

Unfortunately, patients are often discharged from the hospital long before a manic episode has sufficiently resolved only to be followed by readmission shortly afterward. Before discharge the manic patient should have a marked decrease in symptoms and some insight into the illness and show a willingness to continue lithium (260). In addition, the patient's family should be educated to have an understanding of the illness and the importance of maintenance therapy.

4.9.2. Other Treatment Therapies

All the second-generation antipsychotics except lurasidone have FDA indications for the treatment of mania. It is desirable to weigh the patient, measure waistline and obtain a metabolic panel before these medicines are started. The doses recommended are as follows: risperidone, 2–6 mg/day, olanzapine 10–20 mg/day, quetiapine 400–800 mg in divided doses, ziprasidone 80–160 mg/day, again in divided doses, asenapine 100 mg twice daily, and aripiprazole 30 mg/day. The side effect profiles of each are different, as are the presumed modes of action. The major drawback to some of them is weight gain, metabolic syndrome, and the onset of diabetes, but as we have already noted, there seems to be some relationship between bipolar illness and diabetes, independent of medications.

Double-blind, placebo-controlled studies (261–264) have also shown valproic acid to be effective in the treatment of acute mania. Before beginning, a complete blood count and liver function tests are recommended. Depakote (enteric coated divalproex sodium) is a delayed-release tablet that causes less nausea. The goal is to achieve a blood level between 60 and 120 ng/mL (265).

Giving 20–30 mg/kg from the outset can approximate the dose necessary for therapeutic plasma levels. Beginning at this dose apparently results in a shorter time to improvement than does a conventional tapering regimen and entails no greater side effect burden (266). Poorer responses have been demonstrated for plasma levels below 60 ng/mL and, because protein binding begins to become saturated at doses exceeding 100 ng/mL, concentrations of the unbound portion may rise much more rapidly with increasing plasma levels beyond that point (267). Doses should be adjusted if used with other mood stabilizers like lamotrigine.

Carbamazepine XR as well is useful in the treatment of acute mania (268–272) and placebo-controlled studies have shown it to be an effective antidepressant (273, 274). The average daily dose varies across studies from 200 to 800 mg bid, and the average blood level to be achieved varies between 6 and 12 ng/mL. The use of loading doses is not recommended. Before beginning, a complete blood count and liver function tests are desirable because carbamazepine too can produce elevations of liver function tests and reductions in white blood cell and platelet counts in a dose-related fashion. Dose, however, does not predict the rarely seen aplastic anemia or agranulocytosis. Carbamazepine induces its own metabolism, causing the blood concentrations to drop after several weeks so that an upward adjustment of medication is often necessary. Because it induces liver enzymes, carbamazepine may lower valproate levels and these may, in turn, increase if carbamazepine is discontinued. Other drugs also may have their concentrations reduced during treatment with carbamazepine, notably birth control pills and many of the antipsychotics.

The broad efficacy of valproate and carbamazepine does not extend to other anticonvulsants. There is no published evidence that lamotrigine is effective in acute mania and placebo-controlled studies provide no support for gabapentin (275) or topiramate (276).

Although it is said that the anticonvulsants are particularly useful for mixed or dysphoric mania (277–280), one study that compared lithium to valproate did not find this (281). These drugs should be used when a patient is nonresponsive to lithium or when the side effects of lithium are disturbing, particularly in the face of polyuria, weight gain, or acne. Psoriasis can make the use of lithium quite difficult.

McCabe (282, 283) found that both ECT and chlorpromazine were far superior to no treatment in acute mania, when measured by duration of hospitalization, condition at discharge, and social recovery. There were no significant differences between the two treatments, however. He did not have a comparison group of patients treated with lithium, but Black et al. (284) retrospectively compared ECT and lithium and found that patients treated with ECT (unilateral or bilateral) were significantly more likely to show marked improvement, especially in cases of schizoaffective disorder, manic type. A randomized comparison (285) of lithium and bilateral ECT found ECT outcomes to be better in the first 8 weeks but not in the later outcomes. Finally, Mukherjee and Debsikdar (286) reported a very favorable outcome in India in 30 manic patients treated with unmodified ECT. It seemed particularly good for dysphoric mania, severe cases and those featuring catatonia.

4.9.3. Treatment of the Depressive Episode

Various meta-analyses on this topic have reached conflicting conclusions. The controlled trials at this point most strongly support fluoxetine and quetiapine as monotherapy, and combinations of lamotrigine with lithium and of fluoxetine with olanzapine (OFC) (287). Viewed in terms of a ratio of number needed to treat (remission) to number needed to harm (adverse events), a meta-analysis has shown a value of 9 for aripiprazole, for quetiapine and for risperidone. It showed a value of 19 for OFC (288).

Second generation antidepressant monotherapy may be sufficient for bipolar II patients (289–292). For bipolar I patients, antidepressants should be accompanied by a mood stabilizer.

Controlled trials have shown little evidence that the use of SSRI antidepressants with mood stabilizers increase risks for switching (293, 294). On the other hand, evidence from such trials for the efficacy of antidepressants in bipolar disorder is thin (295) though it is present (296). A consensus is developing, that TCA's and SNRI's pose a greater risk for switching than do SSRI's (294, 297, 298).

4.9.4. Maintenance Therapy

Lithium is clearly an effective prophylactic agent and is the "gold standard for maintenance therapy" (299, 300). Not only does it significantly decrease the number of manic episodes, but it also decreases the number of depressive episodes and the likelihood of suicide. This may occur because lithium decreases the number of manic episodes and, since the illness is frequently biphasic or triphasic, it automatically decreases the potential for depressive episodes. Also, the quality of the episodes that do occur is changed (shorter, less severe), and hospitalization is more often avoided. Because mood swings still occur, however, patients on maintenance lithium need to be followed regularly so that the physician can add antipsychotics, an antidepressant, or other drugs if necessary. Lithium can be given in a single bedtime dose that can be either lithium carbonate or a sustained-release lithium. There is some evidence that this reduces lithium's impact on the kidney (301) and it is likely to improve compliance.

The preventative effects of lithium for mania appear to increase steadily at least up to a level of 1.2 mEq/L (302). Prophylaxis against depressive episodes requires a minimum of 0.6 mEq/L.

When manic symptoms reappear during lithium treatment the treating physician should attempt to determine whether they occur despite adequate plasma levels. This may be difficult with an acute admission for mania since symptom breakthrough may have occurred with adequate levels but then resulted in noncompliance. In any event, a single breakthrough does not necessarily signify lithium's ineffectiveness. Mirror image studies have shown that episodes are less severe and frequent after lithium is started than during a period of similar length before it is started (303).

Carbamazepine and valproic acid are also good maintenance therapies, and here, too, the dose for maintenance is the same as that necessary to treat the acute attack. Lamotrigine is more effective against depressive than against manic occurrences and is therefore complimentary to lithium which is more protective against manic than against depressive episodes (304, 305). The side effect profiles of lithium and lamotrigine do not overlap so their use in combination has unique benefits.

The previous course of illness has bearing on prophylactic treatment selection. As anticonvulsants may be more effective than lithium for acute mixed mania, this selectivity may extend to prophylaxis (306). A family history of mania has been associated with better lithium prophylaxis (307–309).

Patients with a rapid cycling pattern are more likely to experience recurrences during prophylaxis than are those with sustained periods between episodes. Because early studies were focused on lithium as the sole prophylactic agent, rapid cycling has come to be regarded as a predictor of poor response to lithium per se (307, 310). However, most comparisons of prophylaxis success rates between those for lithium and those for anticonvulsants have not found a difference (311–313).

All data show that there is a high risk of recurring episodes if lithium maintenance is discontinued, particularly if it is done abruptly, so a sudden cessation of lithium is hazardous (314, 315). As might be expected, those who had been without episodes for the longest period before lithium discontinuation were the least likely to experience relapse. Even with a pregnancy, lithium should be discontinued gradually and the patient followed very closely.

On maintenance lithium, thyroid and renal functions need to be monitored. With carbamazepine and valproate, blood counts and liver function should be monitored. Blood levels should be done one to two times a year.

Jamison and Goodwin (316) have outlined the therapeutic issues surrounding maintenance therapy with lithium, including patient and physician compliance. O'Connell et al. (317) also discussed the relevance of family and psychosocial factors in the outcome of lithium-maintained bipolar patients, as did Clarkin et al. (318). It is important to address these issues when the literature on maintenance therapy is reviewed, there are far more relapses in collaborative treatment studies of multiple investigators than in studies reported by individual therapists treating a cohort of patients. It is definitely a disorder in which the quality of therapy and management make a difference.

It should be noted that stereotactic tractotomy is still being used for the most resistant cases (319–321). Increasing knowledge of the neurocircuitry underlying mood disorder has resulted in a variety of targets for both tractotomy and deep brain stimulation (321).

4.9.5. Side Effects of Antimanic Drugs

The side effects of lithium may be numerous and disturbing to the patient but seldom deleterious to his or her health. Many complain of tremor while on lithium, and this can be treated with 30–80 mg of propranolol in divided doses (322). Improvement, if it occurs, can be seen in 24 hours. Plasma levels correlate with degree of tremor so dosage adjustments may be helpful. Weight gain is also a frequent problem. Almost 50% of patients gain some weight, and weight gains of up to 30 kg have been reported. Patients who develop hypothyroidism, edema, polydipsia, or an increased appetite are more likely to experience weight gain, but it is less likely with plasma levels below 0.8 mEq/L. Patients should be warned not to treat an increased thirst with calorie-laden drinks. Nausea is more likely with rapid increases in plasma levels and may be improved with divided doses taken with meals or with a delayed release preparation. The latter choice may result in diarrhea.

Polyuria and polydipsia are common and concomitant use of SSRI antidepressants raises the risk of these problems (323, 324). The avoidance of multiple dosing may be helpful for this (301, 325). Likewise, polyuria may improve with amiloride at 5 mg twice daily (326). In the long term, usually after 10 years of lithium treatment, tubulointerstitial fibrosis may develop. Risks for this do not appear to be dose related. It is reversible in early stages and these can be detected from increasing creatinine levels. This adds to the importance of at least annual monitoring.

Hypothyroidism is more likely in females, in older patients, in those with early weight gain or with a family history of thyroid disease. Cognitive impairment is more highly correlated with TSH values than with lithium concentrations. Moreover thyroid functioning in the hypothyroid half of the normal range is associated with more affective morbidity (327–330).

Some patients complain of effects on cognitive performance. A meta-analysis has shown that lithium results in small but significant impairment in immediate verbal learning and memory (331). The effects of long-term lithium treatment on psychomotor performance appear to be larger difficulties.

Valproate causes at least as much weight gain as does lithium (304). If this threatens compliance, the alternatives of lamotrigine or carbamazepine are typically weight neutral. Nausea is not infrequent and a histamine-2 blocker may be helpful (332). Increases in ammonia levels are also common (333, 334) and may result in fatigue, cognitive slowing, or sedation. This may progress to an encephalopathy regardless of plasma levels (335–337) so ammonia levels should be checked if such complaints are prominent after therapeutic plasma levels are established.

Women may experience menstrual disturbances (338) and possibly polycystic ovary disease (339) though there has been some controversy over this. Use of valproate during pregnancy carries a much higher risk for congenital malformation than does the use of lithium. Hair loss is also more frequent than with other anticonvulsants. Stevens-Johnson syndrome is no less common than with lamotrigine if recommendations for lamotrigine dose tapering are closely followed (340).

Leukopenia is more likely with carbamazepine than with valproate or lamotrigine (341). Notably, concomitant lithium treatment may serve to correct this (342). Hyponatremia is also more frequently seen with carbamazepine (343).

The metabolic side effects of the atypical antipsychotics are well recognized and a metabolic panel at the onset of treatment is now a standard of care. Aripiprazole and ziprasidone appear to carry the least risks for significant weight gain, followed by risperidone, quetiapine, olanzapine, and clozapine, in that order.

4.9.6. Psychosocial Treatment

Pharmacotherapy has been the principle focus of the research into the management of bipolar disorders. Recognition of the extent to which residual symptoms and psychosocial impairment persist despite the use of mood stabilizers has increased interest in psychotherapeutic approaches. Such therapies have sought principally to stabilize day-to-day activities and to improve coping skills, medication compliance, and the recognition of prodromal symptoms.

The largest number of randomized controlled trials has tested cognitive-behavioral therapy (CBT) modified for application to the bipolar disorders. A recent meta-analysis showed low to moderate effect sizes for clinical symptoms ($d=0.44$), quality of life ($d=0.36$), and treatment adherence ($d=.53$) at the end of treatment (344). Effect sizes for clinical symptoms remained at 6–12 months for treatment ($d=0.43$) but were nonsignificant for the other four clinical outcome categories listed. At no point did CBT significantly increase or decrease treatment costs.

4.9.7. Advantages of Lithium

A recent meta-analysis of 31 studies conclusively showed that the risks of completed and attempted suicide were consistently lower, by approximately 80%, during treatment of bipolar and other major affective disorder patients with lithium compared to those not treated with lithium (345). A significant advantage for lithium treatment persisted when trials were limited to those that were randomized and controlled. Moreover, the ratio of attempted to completed suicide was 2.5 times higher than in lithium treated patients indicating that, when suicide attempts occurred, they had lower lethality in patients who were taking lithium. A randomized, placebo-controlled trial undertaken to assess the anti-suicidal effects of lithium found a strong trend in the expected direction for suicide attempts and a significant difference for completed suicide (346).

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5
Major Depressive Disorder

Barry R. Rittberg, M.D.*

Abstract Major depressive disorder or "unipolar depression" is a common condition likely related to several etiologies. Recent research has focused on the biological underpinnings of major depressive disorder as well as treatment advances, involving both pharmacotherapy and psychotherapy. In this chapter, the epidemiology, clinical picture, biological theories regarding etiology, clinical presentation in primary care and mental health settings, and treatment of major depressive disorder are reviewed. Advances in genetic approaches to understanding the pathogenesis of major depressive disorder will likely result in better and more precise treatments in the future.

The term "unipolar depression" evolved from the concept of a primary affective disorder. Primary affective disorder referred to patients whose first psychiatric disorder was depression and who did not evidence manic or bipolar symptoms. Support for the classification of primary affective disorder derived from the classic study of Cassidy et al (1), and symptoms differentiating depressed patients from controls formed the basis of the disorder. Symptoms which occurred in more than 50% of depressed patients included reduced energy, impaired concentration, anorexia, initial insomnia, loss of interest, difficulty starting activities, worrying, subjective agitation, slowed thinking, difficulty making decisions, terminal insomnia, suicidal ideation or plans, weight loss, tearfulness, slowed movements, irritability, and feeling one will never get well (2). These symptoms continue to form the basis for the diagnosis of depressive states.

Keywords Major depressive disorder · Pharmacotherapy · Psychotherapy · Biology of depression · Epidemiology · Genetic studies

5.1. Definition

The term "unipolar" has been dropped from the official nomenclature of DSM-IV TR and DSM-5 and replaced by "major depressive disorder" (MDD). MDD is characterized by one or more major depressive episodes—2 week or greater periods characterized by a grouping of symptoms including depressed mood, anhedonia, sleep, appetite and psychomotor changes, loss of energy, difficulty concentrating, feelings of worthlessness/guilt and suicidal ideation. Furthermore, MDD is diagnosed if there is no history of mania or hypomania (Bipolar I or Bipolar II) disorder, schizophrenia (schizoaffective disorder), medical cause of the symptoms (i.e., hypothyroidism), and depression due to substances that may cause this syndrome (some antihypertensives or stimulants). A brief depression of less than 2 weeks' duration after a life event is also excluded from MDD (adjustment disorder with depressed mood). Impairment in functioning related to the disorder is required. In the United States DSM 5 is the current standard for classification. Worldwide, the ICD system is used. Persistent depressive disorder (formerly dysthymia) can be a low-grade depression that does not meet symptom criteria for Major Depression. It must be present for more days than not for at least 2 years. A Major Depression may be superimposed on Dysthymia. This is often referred to as a "double depression." Chronic MDD of at least a 2-year duration also falls under the Persistent Depressive Disorder classification.

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B.R. Rittberg, M.D. (✉)
Assistant Professor, Department of Psychiatry, University of Minnesota School of Medicine,
Minneapolis, MN, USA
e-mail: rittb001@umn.edu

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DSM-5 lists several subtypes and course modifies for MDD. "With melancholic features" includes subjects who have a lack of mood reactivity, loss of pleasure from usual activities, distinct quality of the depressed mood, depression worse in the morning, weight loss, excessive guilt, and psychomotor retardation. "With atypical symptoms" is diagnosed if subjects have mood reactivity, over-sleeping, over-eating, rejection sensitivity, and a feeling of leaden paralysis. "With seasonal pattern" is diagnosed if subjects have multiple depressive episodes which usually begin and end at the same time per year. The typical pattern is a winter depression beginning in the fall and ending in the spring. "With psychotic features" is diagnosed if delusions and or hallucinations complicate the mood disorder. These symptoms can be mood congruent or mood incongruent. "With catatonic features" is diagnosed if there are pronounced movement disorders associated with the depression. "With peripartum onset" refers to depression onset during pregnancy or after delivery. Lastly, there is a descriptor of "with anxious distress."

Depression severity can be characterized as mild, moderate, or severe. Determination of severity can be made clinically or by the use of rating scales which had been standardized to determine levels of severity of depressive symptoms over the past week (3–7). Lastly, modifiers also include "in partial remission," in full remission, and unspecified.

5.2. Epidemiology

Two important epidemiologic studies suggest that MDD is quite common and also occurs with high rates of comorbidity (complicated by the presence of other psychiatric disorders) (8, 9). The national comorbidity survey reported lifetime prevalence of MDD of 12.7% in males, 21.3% in females and overall 17.1%. The national comorbidity survey replication study showed similar data. Thus MDD is a common condition and occurs in women twice as frequently as men. In contrast, bipolar mood disorders are estimated to have a lifetime prevalence of 6–8% including the "bipolar spectrum" disorders. MDD occurs in all cultures and affects all age groups. Childhood and late adult onsets are common, and the mean age of onset is generally in the 30s.

5.3. Clinical Picture

Although the criteria for a major depressive episode is 2 weeks or greater, most episodes last much longer and the mean duration of an episode of MDD is generally 6–9 months. Individuals who have one episode are 50% likely to have a recurrence. Individuals who have three or more episodes are 90% likely to have further episodes. Chronic MDD is 2 years or greater of depression and about 20% of MDD patients have chronic MDD. Another type of chronic depression is dysthymic disorder. Most patients with dysthymic disorder ultimately experience one or more major depressive episodes. This condition has been termed "double depression" (10), and most individuals with dysthymic disorder will ultimately experience one or more major depressive episodes. These are diagnosed as persistent major depression with persistent major depressive episode or with pure dysthymia syndrome, respectively.

As mentioned above MDD is quite commonly complicated by other psychiatric conditions. These include panic disorder and other anxiety disorders, substance use disorders including alcoholism, eating disorders, and other major psychiatric conditions (Axis I disorders). Axis II conditions or personality disorders also frequently complicate MDD. The general rule is that individuals with comorbid disorders are more severely ill and more difficult to treat than those who do not have comorbidity.

Suicide and suicide attempts are unfortunate complications of MDD. The exact rate of suicidal behavior among MDD patients is unknown. Some estimates cite about 15% of patients who experience severe depression will ultimately die by suicide. The rate of suicide in the United States is approximately 10–12 per 100,000 individuals per year and at least half of the approximate 30,000 suicides in the United States annually are related to depression. In contrast to concerns in the lay press, research studies suggest that suicide rates in adults are decreased with treatment with modern antidepressants (11, 12).

Depression can complicate medical conditions and if one has a medical condition the depression is frequently worse. Again it is important to rule out possible medical causes of depression, especially in the instance of a patient who has a depressive syndrome and an ongoing medical condition that may be associated with a mood disorder.

Depression in the elderly is of particular relevance in individuals who may be experiencing cognitive effects. The differential diagnosis of depression in a patient who is suspected to have Alzheimer's disease needs to be carefully considered.

Depression can also occur in children and adolescents. Bipolar disorders frequently have earlier ages of onset, and the differential diagnosis of depression in younger individuals should include consideration of bipolar disorder.

5.4. Depressive Subtypes

As noted above, there are several subtypes of depression. About 20% of patients with MDD will have chronic depression and about 25% will meet criteria for a diagnosis of depression with atypical features.

Some of these conditions have treatment implications. For example, chronic depression is more difficult to treat than acute single episode depression and takes longer to respond and higher antidepressant doses to affect a response. Recurrent depression requires maintenance therapy in order to reduce the likelihood of recurrence. Melancholic features suggest that the patient will not likely respond to placebo and will require aggressive treatment. Patients with depression with psychotic features are best treated with electroconvulsive treatment or combination of an antidepressant and antipsychotic medication. Patients with atypical features do not respond well to tricyclic antidepressants and respond better to monoamine oxidase (MAO) inhibitors and also to treatment with selective serotonin reuptake inhibitors (SSRIs).

There is no one characteristic of major depressive disorder. In fact, MDD is a collection of patients who likely have different etiologies to their condition, different clinical courses, and different symptom profiles. One patient may be anxious and agitated and sleepless and another patient may have psychomotor retardation and be over sleeping. Suicidal behavior may be overt in some patients and hidden in others. Some patients have profound comorbidity and some patients only have depressive symptoms. Thus it is impossible to characterize a single type of presentation or symptomatology.

5.5. Etiology

The etiology of major depressive disorder is still unknown. Factors that are thought to play a role in the genesis of MDD include genetic and familial factors as well as negative life experiences. Evidence for both environment and genetics as having a role in the etiology of depression is supported by various studies in the literature (13). The advent of the human genome project will likely go a long way in clarifying the relationship of genetic factors to at least some depressive disorders. Recent genetic research has looked at the role of epigenetics. This refers to the "heritable changes in gene expression that are not encoded by the DNA itself" (14). A recent paper (15) found abnormalities in promoter DNA methylation in the brains of suicide victims. Methylation is a mechanism which helps to turn off and on gene expression. It is likely that both environmental and genetic factors combine to play a role in subjects to produce clinical depression. Thus one might view some individuals as being genetically prone to having depression and who will then develop this depression if confronted with serious negative life events. It is also clear that individuals who have ongoing depression do not tolerate negative life events well and often worsen in the aftermath of the negative life event.

5.6. Biological Theories of Depression

Early theories of the biology of depression were based on the fact that effective antidepressants blocked the presynaptic neuronal reuptake, of the monoamines norepinephrine and serotonin. This led to the speculation that one or more monoamines were responsible for depression by their relative deficit. The advent of SSRIs led to the theory that serotonin dysregulation was involved in the pathogenesis of depression. This theory was based on the notion that low levels of serotonin in the brain might be the cause of depression, since the effect of SSRIs was to increase serotonin neurotransmission in the brain (16).

Recent theories of depression have looked at abnormalities in the HPA axis, which includes the hypothalamus, the pituitary gland, the adrenal gland, and elevated levels of cortisol. In depression-prone persons, there seems to be an overactive HPA axis. This may be the result of early life negative events. The cortisol feedback loop is insensitive, and hence there is less inhibition of cortisol release. The high levels of cortisol are toxic to pyramidal cells in the hippocampus and result in cell death and atrophy of the hippocampus. Evidence to support this theory comes from studies in animals that were subject to parental deprivation as infants and demonstrate dysregulation of the HPA axis (16). Furthermore, patients with severe depression have elevated cortisol levels and have smaller hippocampus than controls (17, 18). Genetic linkage studies in MDD have failed to identify reliable gene candidates. Polymorphisms have been identified for the serotonin transporter gene, monoamine oxidase type A, tryptophan hydroxylase, noradrenaline transporter, adrenaline, and noradrenaline receptors, as well as dopamine receptors and transporters. These are being studied as candiates for association with depression (19).

Recent reports of ketamine (a partial NMDA receptor antagonist) causing a rapid decrease in depression symptoms have focussed research on the NMDA receptor. Ketamine is an anesthetic that, in this case, is used far below the anesthetic dose to treat depression (20, 21).

Mitochondrial dysfunction and inflammation-induced neural degeneration are all active theories in the etiology of depression (22).

5.7. Laboratory Studies

There are no definitive laboratory tests that reliably demonstrate that one group of depressed patients differs from another group of depressed patients or that depressed individuals can be reliably differentiated from normals or from nondepressed individuals (23). Laboratory tests studied throughout the years include the dexamethasone suppression test which showed elevations

of cortisol response after dexamethasone administration in a greater number of depressed patients than controls. However, this test failed to reliably demonstrate differences between patients and controls and is no longer widely used, even in research settings. Other tests reported to be abnormal are a blunted TSH response to TRH. This test is also not currently in clinical use.

Depressed patients frequently have sleep abnormalities and a striking sleep abnormality among depressed patients is shortened REM latency. This finding has been replicated but is of little diagnostic utility

One of the problems with laboratory testing in depressed patients is that major depression itself is likely a very heterogeneous disorder. This makes the likelihood of finding a test that is reliable and can differentiate depressed patients from nondepressed individuals or subtypes of depressed patients from each other difficult.

5.8. Presentation of Depression in the Primary Care Setting

Most patients with depression have their initial medical encounter in a primary care setting. Unfortunately the data regarding recognition of depression in primary care settings has been stable and disappointing over the past several decades. The "50% rule" applies: that is, 50% of individuals with depression are diagnosed in primary care settings and 50% are not. Of the 50% who are diagnosed only 50% are treated. Of the 50% who are treated only 50% are adequately treated (24). It is quite likely that depression would be ascertained more reliably in primary care settings if rating scales to detect major depression such as the Beck Depression Inventory (3), the PHQ-9 (5), or the Quick Inventory of Depressive Symptoms (7)—patient self-rating scales—were applied uniformly to patients presenting in primary care settings, just as a blood pressure and weight are uniformly assessed in such patients.

Depression can present in primary care settings in a multitude of ways. The patient may have seen an advertisement regarding depression in the news or television and presents with a clear complaint and self-diagnosis of depression. Many patients will present with a psychic complaint of anxiety rather than depression. However, many more patients will present with indefinite physical complaints such as fatigue and loss of energy or aches and pains in various organ systems (25). The primary care physician needs to be well attuned to these various presentations of depression so that a proper diagnosis can be made, a proper workup for these patients performed, and a proper treatment plan implemented. Mental illnesses still carry a great deal of stigma regarding their diagnosis. Thus it is important for the primary care physician to present the diagnosis firmly but cautiously as well as optimistically regarding treatment outcome.

The workup for patients suspected of having depression should include a careful history to determine if previous episodes have occurred, a family history to determine if individuals in the family also suffered from depression or bipolar disorder, a physical exam, and a series of laboratory tests, especially a TSH or thyroid assessment. There are many medical causes of a depressive syndrome and many types of depressive disorders. Thus, the clinician needs to carefully consider the differential diagnosis before implementing treatment.

Important conditions to rule out before a diagnosis of MDD is made include the common medical conditions that are associated with MDD, bipolar disorders, anxiety disorders, and substance use and alcohol disorders. The common medical conditions can be simply ruled out with simple laboratory testing—complete blood count to rule out anemia and thyroid screen to rule out hypo- or hyperthyroidism. Other laboratory tests may be indicated if there are particular symptoms or signs that suggest the need for such testing. Since some medications may cause depression, a review of medication changes in the patient in relation to depressive onset is important. Bipolar disorders can be ruled out by asking about hypomanic or manic symptoms occurring prior to or after depressive episodes. About 5% of patients who are experiencing their first depressive episode are bipolar, and this diagnosis usually cannot be made until the patient exhibits hypomania (26). Factors that suggest a patient may be bipolar include frequent and multiple depressive episodes, a family history of bipolar disorder, and an early age of onset. A screening tool, the "Mood Disorders Questionnaire," may also be useful (27). Anxiety disorders frequently complicate mood disorders and depression frequently complicates anxiety disorders. Asking about panic attacks, level of anxiety and its duration in relation to the depressive symptoms, and obsessive compulsive behavior is useful. Substance use disorders and alcohol abuse/dependence are not always correctly identified through history taking as patients frequently deny these conditions. A substance use and alcohol history is important to ascertain, and urine toxicology testing may be helpful if substance use is suspected.

5.9. Presentation of Depression in a Mental Health Setting

In contrast to the situation in primary care, most individuals who are seen in mental health settings for depression have already been diagnosed or are undergoing treatment which is not successful (treatment resistance). In such cases the diagnosis of depression is clearer than in primary care settings. However, the differential diagnosis still needs to be applied and the depression carefully delineated as a major depressive disorder versus a bipolar disorder or a medical disorder with depression. Careful alliance between the mental health practitioner and the patient's primary care physician is important to ensure that the differential diagnosis of the depression from a medical perspective has been satisfactorily determined.

5.10. Principles of Treatment

The principles of treatment of major depressive disorder have been well established over the past two decades. The goal of treatment is to achieve remission and also recovery. Remission is defined as a sufficient absence of depressive symptoms so as to generate a rating of seven points or less on the 17 item Hamilton Depression Rating Scale (4). The Hamilton Depression Rating Scale is a clinician rated, standardized scale for assessing depression severity. Recovery currently is defined by at least two months of a remitted state. The rating scales noted above [Beck Depression Inventory-BDI (3), Quick Inventory of Depressive Symptoms –QIDS (7), and the Patient Health Questionnaire-PHQ-9 (5)] are self-rating scales and are also useful for the patient and clinician to determine the clinical state of the ongoing depression. Remission on the BDI is 9 points or less, on the PHQ-9 is 4 points or less, and on the QIDS is 5 points or less. Depression needs to be considered a lifelong disorder since it is often chronic and frequently recurrent. In situations when patients can monitor their mood with a rating scale, the degree of depression can be easily ascertained by the clinician from the patient self-ratings.

The next principle of treatment is to effectively treat the presenting episode so that it does not relapse. In order to do this patients need to be treated through an acute treatment phase, usually of about 12 weeks' duration and achieve at least a response to treatment in that period of time. Many studies support the notion that if antidepressant treatment is stopped at the end of the acute treatment phase there will be a higher relapse rate than if treatment is continued for 6–9 months longer. Thus, the initial episode of depression should be treated to remission and should have the treatment continued for approximately a year (28, 29). In instances of recurrent depression or chronic depression, current recommendations are for maintenance treatment for at least several years if not for a lifetime. Recall that if individuals have recurrent depression they are highly likely to have further episodes of recurrence. In instances of chronic depression the depression may relapse if long-term treatment is not applied. When treatment is to be terminated it is always best to taper treatment and have patients keep a mood calendar to determine if they are having a recurrence of symptoms during the taper of the treatment. If symptoms recur then the treatment needs to be resumed at the previous dose. Interestingly, studies of both pharmacotherapy and psychotherapy support the notion of the need for continuation and maintenance treatment for depression (30, 31).

Treatment must be given for an adequate duration of time and also at an adequate dose. There is no consensus definition of adequate duration, but 8–12 weeks of treatment is usually recommended. The STAR*D study involved several thousand patients with major depression who were treated mostly in primary care settings (32, 33). Most of the patients were being treated in their first episode of depression. This study involved "guided" treatment in that the treating clinician was advised by the study monitor regarding dose adjustment if the patient failed to achieve remission during the ongoing acute treatment phase. Assessment was made by use of the QIDS and remission of symptoms was the goal of treatment. About 28–33% of patients achieved remission with treatment from an SSRI in the acute treatment phase. Subsequent treatments for this population increased the remission rate overall to approximately 60% after a number of treatments were administered. This study differs from current clinical practice in a number of ways. First of all subjects were assessed via rating scales and clinicians were notified to increase the dose if the optimal treatment outcome was not achieved. Patients had a second treatment trial if the first treatment did not produce remission, and if that treatment did not produce remission then subsequent treatments were applied. In typical clinical practice subjects do not have monitoring of their moods through rating scales nor is there someone to guide the dosage for the clinician. However, these principles of treatment should be applied to clinical practice in order to achieve an optimal outcome for depressed patients.

5.11. Treatments for Depression

Treatment of depression can be separated into three major categories: psychotherapy, pharmacotherapy, and physical therapies. Although logic dictates that combined psychotherapy and pharmacotherapy might provide an optimal outcome, data to support this notion are generally not found in research studies.

5.11.1. Psychotherapy

Psychotherapies that have been studied for major depression and shown to be effective include cognitive behavioral psychotherapy (CBT), interpersonal psychotherapy (IPT), and behavioral activation (BA). The modern trend is to have clinicians administering these therapies trained and certified in the therapies they are administering. The therapies noted above are brief—on the order of 20 weeks—and administered according to a "treatment manual." These three types of psychotherapies have been shown to be as effective as antidepressants in mild to moderate outpatient depression (34–36). CBT, IPT, and BA have all been shown to be effective in reducing relapse and recurrence in depressed patients (37–40).

5.11.2. Pharmacotherapy

We recommend pharmacotherapy if the presenting depression is of moderate or greater severity. Pharmacotherapy is also a logical choice if the patient has a history of recurrent depression or chronic depression. If the patient has a severe depression, treatment with pharmacotherapy or electroconvulsive therapy may be the best treatment. If the patient has psychotic depression the combination of an antidepressant and antipsychotic medication is helpful, although electroconvulsive therapy is the optimal treatment for this condition.

There are several types of pharmacotherapies. The older antidepressants tend to be less safe than the newer antidepressants and therefore the newer antidepressants are preferable as starting treatments (see Table 5.1). The newer antidepressants include the selective serotonin reuptake inhibitors or SSRIs (see Table 5.2). These compounds replaced the tricyclic antidepressants as first choice treatments for depression in the 1990s. Because of their overall safety they remain the treatment of choice for the initial treatment of a depressed patient.

As a general rule all antidepressants have equal efficacy and classes of antidepressants or medications within a class differ only in their side effect profiles. The classes of antidepressants include the SSRIs (fluoxetine, sertraline, paroxetine, fluvoxamine, citalopram, and escitalopram). Serotonin reuptake inhibitors that also have serotonin receptor effects include trazodone, nefazodone, vilazodone, and vortioxetine. Mirtazapine is not a reuptake inhibitor, but has direct receptor effects on serotonin and norepinephrine subtypes. The serotonin and norepinephrine reuptake inhibitors include venlafaxine, desvenlafaxine, and levomilnacipram. The older tricyclic antidepressants are also serotonin and norepinephrine reuptake inhibitors. The tricyclics include amitriptyline, imipramine, doxepin, nortriptyline, protriptyline, trimipramine, and desipramine. Tranylcypromine, phenelzine, isocarboxazide, and selegiline are monamine oxidase inhibitors.

TABLE 5.1. Common antidepressants and their usual doses.

Drug	Dosage	Comments
Amitriptyline	50–300 mg	Converted to nortriptyline
Imipramine	50–300 mg	Converted to desipramine
Doxepin	50–300 mg	
Nortriptyline	50–200 mg	
Desipramine	50–200 mg	
Protriptyline	10–40 mg	
The above are tricyclic antidepressants and share common side effects such as dry mouth, constipation, tachycardia, orthostatic hypotension, sedation, weight gain, and blurring of vision. These medications can also be lethal in overdose and have numerous cardiac effects. Blood level monitoring may be useful.		
Isocarboxazide	20–60 mg	
Tranylcypromine	20–60 mg	
Phenelzine	45–90 mg	
Selegiline transdermal system	6–12 mg/24 h	Administered as a patch
The above are monoamine oxidase inhibitors and have several food and medication prohibitions in order to prevent severe hypertensive episodes.		

TABLE 5.2. Newer antidepressants and their doses.

Drug	Doses (mg)	
Fluoxetine	20–60	
Sertraline	50–200	
Paroxetine	20–60	
Citalopram	20–40	
Escitalopram	10–20	
Venlafaxine	75–375	Hypertension can occur at doses above 300 mg
Duloxetine	60–120	
Mirtazapine	15–60	
Nefazodone	300–600	
Bupropion	150–450	Seizures can occur at doses above 450 mg
Trazodone	100–600	Priapism can occur in male patients
Vilazodone	40	
Vortioxetine	10–20	
Levomilnacipran	40–120	
Desvenlafaxine	50–100	

Within the SSRI class the most common side effects are GI disturbances, especially nausea, on initiation of the treatment. In anxious depressives, anxiety may temporarily worsen and starting with lower than usual doses in anxious depressives is recommended. About 15% of patients treated with SSRIs develop insomnia and about 15% experience sedation. Weight gain is usually not a problem with the SSRIs with the exception of paroxetine, and a small percentage of patients will gain a significant amount of weight with this compound. A common late appearing side effect associated with the SSRIs is sexual dysfunction. This side effect occurs in up to 50% of women and perhaps 25% of men and is the most common reason for discontinuation of this class of medication during long-term treatment. The SSRIs are safe in overdose and reduce suicidal behavior in adult depressed patients. Only one SSRI, fluoxetine, has been shown to be effective in the treatment of children with depression. All of the SSRIs are frequently used in the elderly. The SSRIs commonly have drug interactions involving the P450 2D6 enzyme system. All SSRIs with the exception of fluoxetine are associated with a flu-like syndrome on rapid discontinuation and paroxetine has the most marked discontinuation syndrome. As a class, SSRIs show efficacy in a number of anxiety disorders and many are FDA approved for treatment of panic disorder, social phobia, generalized anxiety disorder, post-traumatic stress disorder, and obsessive compulsive disorder. Because of the simplicity associated with their use, overall safety and broad spectrum efficacy, these antidepressants have become the first-line choice for treatment of depression.

The newer antidepressants listed above do not have similar side effects. Venlafaxine, desvenlafaxine, levomilnacipran, and duloxetine are serotonin and norepinephrine reuptake inhibitors. Their common side effects include nausea on initiation of treatment. Sexual dysfunction appears to be less in women with duloxetine than with venlafaxine but venlafaxine has less inhibitory effect on the P450 2D6 enzyme system than does duloxetine. The discontinuation syndrome associated with venlafaxine is much more marked than that for duloxetine and tapering of these compounds is recommended if they are to be stopped. Sustained hypertension is associated with high dose treatment with venlafaxine but has not been associated with treatment with duloxetine, even though duloxetine may have a more potent effect on the norepinephrine transporter system than venlafaxine. Venlafaxine is FDA approved for major depression, generalized anxiety disorder, and panic disorder. Duloxetine is FDA approved for major depression and diabetic peripheral neuropathic pain, and is approved in some European countries for stress induced urinary incontinence. Desvenlafaxine, the active metabolite of venlafaxine, is marketed as a separate agent. It has an FDA indication for depression only. It is a timed release product with an effective dose of 50–100 mg per day. Desvenlafaxine can also have an unpleasant withdrawal syndrome.

Levomilnacipran is also a norepinephrine and serotonin reuptake inhibitor. It has greater effect on norepinephrine than serotonin reuptake. It also has greater effect on norepinephrine than venlafaxine and desvenlafaxine including the risk of hypertension. It is not associated with weight change (41). Levomilnacipran has a wide dose range of efficacy with a dose range of 40–120 mg per day all showing greater efficacy than placebo. The usual starting dose is 20 mg per day with dose increases every two days until desired dose is reached.

The mechanism of action of bupropion is not clearly understood, although it is thought to have a role in dopamine metabolism and is clearly not a serotonin reuptake inhibitor. Bupropion is not associated with weight gain, sexual dysfunction, or a discontinuation syndrome. It is one of the most activating of the antidepressants currently approved and should not be given close to bedtime as it can cause insomnia. Seizures have been reported with higher dose treatment with bupropion and there is a dosage limit of 450 mg with this compound. It is not a particularly effective drug in treatment of comorbid anxiety disorders, although the anxiety associated with depression responds well to treatment with bupropion. Bupropion is FDA approved for major depression and for smoking cessation.

Mirtazapine is one of the most sedating of the newer antidepressants. Mirtazapine has a complicated mechanism of action and affects both serotonin and norepinephrine systems. Its effects on histamine receptors result in sedation, particularly at low doses, and weight gain has also been reported with mirtazapine. Mirtazapine has a low rate of sexual dysfunction and mild effects on the P450 2D6 isoenzyme system. It is unclear if mirtazapine has a discontinuation syndrome. This compound is only approved for major depression by the FDA.

Trazodone is moderately sedating and the major clinical use of trazodone is to combat insomnia associated with SSRI treatment. At higher doses trazodone is an effective antidepressant. Reports of priapism in male patients have resulted in our not recommending the use of trazodone in men. Trazodone is FDA approved for treatment of major depression.

Nefazodone also has a complicated mechanism of action and affects the serotonin postsynaptic receptor with mild serotonin and norepinephrine reuptake inhibition. Nefazodone affects the 3A4 liver isoenzyme system. Its major side effects are sedation and there is a need for complicated dose titration to achieve a therapeutic dose range. Nefazodone does not appear to cause weight gain, sexual dysfunction, or a discontinuation syndrome. Cases of liver toxicity have been reported with nefazodone and the use of this the drug is infrequent in clinical practice. Nefazodone is approved by the FDA for treatment of major depression.

Vilazodone is a serotonin reuptake inhibitor and a 5-HT_{1A} partial agonist. It is reported to have low sexual side effects and does not cause sedation and weight gain (42). The usual dose of vilazodone is 40 mg per day. It needs to be started at 10 mg and titrated up to prevent gastrointestinal side effects. Absorption is improved when taken with food (43).

Vortioxetine is a serotonin reuptake inhibitor that also has effects on specific serotonin receptors (5-HT_{1A}, 5-HT_{1B}, 5-HT_3, and 5-HT_7). It is also purported to have low incidence of sexual side effects and no effect on weight (44). The starting dose is 10 mg, which is increased to 20 mg. It has a very long half-life of 66 hours, therefore needing a 3-week washout before using an MAOI.

The tricyclic antidepressants have a myriad of side effects because of their multiple receptor affinities. They not only affect serotonin and norepinephrine reuptake systems but also have effects on histamine, anticholinergic, and muscarinic receptors. These receptor effects result in side effects such as dry mouth, blurry vision, dizziness, constipation, orthostatic hypotension, increased heart rate, weight gain, and sedation. The tricyclic antidepressants are not safe in overdose and 1.5 g or greater of a tricyclic antidepressant taken in a single overdose can be lethal. These drugs are FDA approved for major depression but also are frequently used off label in pain situations and also have effects in panic disorder. Prior to the advent of the SSRIs in United States the tricyclic antidepressants were first-line treatments. However, their multiple side effects and the lethality in overdose have resulted in a considerable diminution of their use.

The MAO inhibitors were among the first antidepressants introduced in the United States. These drugs inhibit the enzyme that degrades monoamines. Their early clinical use was associated with notable side effects of acute hypertensive crisis and stroke resulting from ingestion of tyramine containing foods or certain medications. MAO inhibitors not only inhibit monoamine oxidase in brain but also in the GI tract where tyramine in foods is normally detoxified by the digestive system. Blockage of this detoxification results in tyramine entering the bloodstream, releasing norepinephrine and causing acute hypertension. Thus tyramine containing foods and certain medications need to be avoided when being treated with MAO inhibitors. MAO inhibitors are approved by the FDA for treatment of major depression. Phenelzine has also been shown to be effective for the treatment of panic disorder and tranylcypromine for the treatment of bipolar depression. Recently selegiline has been formulated to be administered in a transdermal patch. The use of this patch avoids the GI system inhibition of monoamine oxidase and therefore low doses of the patch permit the dietary intake of tyramine containing foods. Oral selegiline is FDA approved for the treatment of Parkinson's disease. Antidepressants and other medications are prohibited during treatment with MAO inhibitors because of the risk of causing a hypertensive crisis or a serotonin syndrome.

5.11.3. Physical Treatments for Depression

Several physical treatments are important in the treatment of depression. These include bright light therapy, electroconvulsive therapy (ECT), vagus nerve stimulation treatment (VNS), repetitive transcranial magnetic stimulation (rTMS), magnetic seizure therapy (MST), and deep brain stimulation (DBS). Of these treatments only ECT, VNS, and rTMS are currently approved treatments in United States and bright light therapy is widely used. MST and DBS are currently experimental (45, 46).

Bright light therapy was developed to treat seasonal mood disorder, particularly winter depression. This depression, which can occur in patients with major depression or bipolar depression, is frequently characterized by oversleeping. Research studies support the use of bright light therapy, usually given in the morning, for improvement of depressive symptoms in these subjects (47). Whether subjects with recurrent winter depression might also be treated with a maintenance therapy is an important consideration. Light boxes and dawn simulator devices are available through several commercial outlets and usually do not require a prescription.

ECT was developed in the 1930s as a treatment for schizophrenia under the mistaken assumption that patients with epilepsy did not develop schizophrenia. Early use of this treatment resulted in the finding that ECT was much more effective for individuals with severe depression than for patients with schizophrenia and the treatment has remained in use as an effective treatment for individuals with severe and treatment resistant depression, and is the treatment of choice for patients with psychotic depression and mood disorders complicated by catatonic features. The modern use of ECT involves administration of anesthesia. The patient is usually sedated with a brief acting anesthetic and then given succinylcholine in order to temporarily paralyze muscles so there is no pronounced physical movement during the convulsion. The treatments are usually administered 3 days a week and an average of 8–10 treatments is typical to improve a severe depressive state. Some patients relapse quickly after ECT is stopped and may require ECT be given on a long-term basis for maintenance treatment. Antidepressant medication should be started after a series of ECT has been administered in order to reduce the likelihood of relapse (48). Side effects of ECT include confusion which usually clears after each treatment and permanent memory loss for some of the days when the treatments have been administered.

VNS was approved by the FDA for treatment of resistant depression. VNS had previously been approved for treatment resistant epilepsy and its use over the years in epileptic patients has resulted in a good deal of knowledge regarding the side effects of VNS treatment. VNS involves the surgical implantation of a pulse generator into the chest wall and attachment of the wire leads from this pulse generator to the vagus nerve. The pulse generator produces a current which is transmitted into the brain and affects a number of brain areas that are thought to be important in relation to mood disorders. As VNS involves a surgical procedure, there is a small- about 1%- risk of surgical complications including pain or infections at the surgical site and care needs to be taken that the recurrent laryngeal nerve is not severed during the surgical procedure. When the device is activated

(usually on for 30 seconds every 5 minutes), the patient may experience voice alteration, cough, shortness of breath, or neck pain. The effect of VNS is not immediate and it often takes 6 months to a year to demonstrate improvement in depression (49). Patients undergoing VNS treatment are ones who have failed at least four antidepressant treatments and are among the most severely treatment resistant patients. A study of patients who were not implanted with VNS but had similar treatment failure histories revealed that only about 10% of such patients improved after 1 year of usual treatment in the community and the improvement in these patients was usually not sustained (50). In contrast, with VNS therapy about a third of the patients markedly improved, about a third of the patients improved somewhat, and about a third of the patients did not change after 1 year and the improvement noted in patients tended to be sustained once it occurred (49).

The FDA has approved tTMS for those patients with major depression who have failed one adequate trial of an antidepressant. rTMS involves the placement of an electromagnet on the outside of the head near the left frontal area of the brain. This magnet generates a current in the superficial layer of the cerebral cortex. Depending on the frequency of the magnetic pulses, it can stimulate or inhibit neuronal activity in that area of the brain. rTMS has been employed experimentally for patients with treatment resistant depression and the results of these research studies show that about a third of the patients will respond in a 3-week period compared to about 10% of patients who are treated with a "sham" treatment (51, 52). rTMS is administered five days a week for about 45 minutes per session. Data suggests that rTMS is ineffective in those patients who have failed ECT or who have psychotic symptoms with their depression.

The other treatments listed above—MST and DBS—are experimental at this time. Magnetic seizure therapy was developed as an alternative to ECT. High-frequency electromagnetic pulses are delivered to the brain to induce a seizure. It causes less cognitive impairment than ECT, but still requires muscle relaxation and general anesthesia (46).

Deep brain stimulation (DBS) is experimental. It involves implanting electrodes into specific brain areas. Stimulation with a pacemaker-like device has shown promise when the electrodes have been placed in the subgenual cingulate, ventral anterior internal capsule, and the nucleus accumbens. Open, unblinded studies have shown promise. Double-blind placebo controlled trials need to be completed (46).

5.11.4. Treatment-Resistant Depression

About 70% of patients who undergo treatment for a depressive episode respond, and about 30% have a remission of symptoms during the acute treatment phase. Patients who do not respond or remit might be considered treatment resistant. There is no uniformly agreed upon definition of treatment resistant depression, but the more treatment trials a subject fails the less likely they are to respond to a subsequent treatment trial. As noted above, ECT and VNS are usually reserved for patients who have failed multiple treatments because they are more invasive than other treatments.

Failure to respond to treatment may be due to many factors, including incorrect diagnosis, too short a treatment trial, or treatments being applied at too low a dose to be effective. Diagnostic issues involve whether the patient is bipolar or has major depression, or whether there is an underlying undiagnosed medical cause for the depression (thyroid disease, tumor, stroke — to name a few). Generally, treatments should be given at higher than starting doses and for at least 8 weeks before the lack of response is considered treatment resistance. Some patients are not truly treatment resistant but cannot tolerate effective treatment doses because of side effects—the "treatment intolerant" patient.

The strategies for approaching a treatment resistant patient involve assessing the patient's history and medical evaluation in order to clarify diagnostic issues and to review the treatment history for type of medication, duration and dose of treatment. The next step is to apply a treatment from another class—presumably a different mechanism of action might be more effective. Augmentation involves addition of a treatment to an ineffective treatment. Common augmentation strategies involve the addition of lithium carbonate or thyroid hormone to medications that have not been effective. Recent research suggests that the addition of an atypical neuroleptic to patients who are not responding to treatment with an SSRI produces a rapid response in the majority of patients (52, 53) Both aripiprazole and quetiapine have been FDA approved as augmenting agents*.

Switch strategies involve selecting a treatment which may have a different mechanism of action than the treatment which has failed—such as switching from an SSRI to an SNRI or to an MAOI.

5.11.5. Other Treatments

Depression often occurs as an episode and has a beginning and an end. Thus, depressed patients may respond to time. The finding that a treatment is effective for depression is therefore quite dependent on placebo controlled studies. Many "treatments" for depression have not been found to be effective when studied in a controlled manner. For example, St. John's Wort was in wide

*Editor's note: Brexpiprazole is an atypical antipsychotic that was approved by the FDA in 2015 as an adjunct for treatment of major depression.

popular use several years ago, but a controlled study later demonstrated that it was not effective in moderately depressed patients (54). Exercise and diet are important for general medical health and likely have positive effects in depression but are not likely to be effective for more moderate depressive states. Psychotherapies need to be further studied to demonstrate their efficacy, and many have passed the test. Whether other psychotherapeutic modalities are effective remains for future evaluation

5.12. Summary

Major depression is a common condition which is likely determined by several etiologies. In clinical practice, depression is underdiagnosed and undertreated. However, several treatments have been shown to be effective for alleviating depressive symptoms. Further research in the genetic basis and molecular determination of some depression may well lead to more effective treatments for this condition. Until that time, however, patients with depression should be encouraged to monitor their clinical condition with self-rating scales and contact their clinician for changes in their treatment should their condition change.

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6
Schizophrenia

S. Hossein Fatemi, M.D., Ph.D., FACPsych and Timothy D. Folsom, M.S.

Abstract In this chapter, we discuss history, current diagnostic criteria, epidemiology, genetics, etiology, clinical signs and symptoms, laboratory investigations, differential diagnosis, pharmacological and behavioral treatment modalities, prognosis and course of illness for schizophrenia. The emphasis in this chapter is the etiopathogenesis and relevant biological treatments for this disorder.

Keywords Schizophrenia • Etiology • Treatment

6.1. History

Schizophrenia is a debilitating disease of the brain which has been described by various physicians for centuries (1). Hippocrates referred to paranoia as a potential antecedent of present day psychosis (1). Aretaeus of Cappadocia referred to a form of mental illness he called insanity (1). Benedict Morel referred to one of the earliest descriptions of schizophrenia as démence précoce (precocious dementia) or deterioration of cognition in the adolescents (1, 2). Karl Ludwig Kahlbaum described catatonic symptoms as early as 1874 (3). Ewald Hecker was the first psychiatrist to refer to disorganized symptoms of schizophrenia as hebephrenia (4).

However, the greatest and most methodological and comprehensive description of schizophrenia was heralded by the German psychiatrist Emil Kraepelin who referred to this disease as dementia praecox and separated it from manic depressive psychosis (5). Indeed Kraepelin's predecessor Wilhelm Griesinger (6) of Berlin's Charité Hospital had already considered psychiatric disorders such as schizophrenia as brain disorders and influenced later psychiatrists on the importance of the organicity of schizophrenia (1) and other psychiatric diseases. Kraepelin's distinction between bipolar psychosis and dementia praecox with the latter disease, being an early onset psychosis which affected cognition permanently and had a poor outcome, opened the way for a true diagnosis of schizophrenia (1, 7).

Eugen Bleuler, another leading figure in the 20th century psychiatry, coined the term schizophrenia to describe the affective disturbance, the ambivalence and sense of isolation (autism), and associative (cognitive) disturbances observed in patients with dementia praecox (8). Bleuler also described schizophrenia as less of a dementing illness with more optimistic prognosis than Kraepelin had suggested (7, 8). Finally, Kurt Schneider, provided the concept of first and second rank symptoms (Table 6.1), to describe schizophrenia. It is now clear that while these symptoms are helpful in diagnosis of schizophrenia, that they are not specific to this disorder.

S.H. Fatemi, M.D., Ph.D., FACPsych (✉)
Associate Chair for Neuroscience and Translational Research, Bernstein Endowed Chair in Adult Psychiatry, Professor, Departments of Psychiatry and Neuroscience, University of Minnesota School of Medicine, Minneapolis, MN, USA
e-mail: fatem002@umn.edu

T.D. Folsom, M.S.
Junior Scientist, Department of Psychiatry, University of Minnesota School of Medicine, Minneapolis, MN, USA
e-mail: folso013@umn.edu

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TABLE 6.1 Schneider's Symptoms.

First rank	Second rank
Audible thoughts	Depressive or euphoric mood changes
Voices heard arguing	Emotional blunting
Voices heard commenting on one's actions	Perplexity
The experience of influences playing on the body	Sudden delusional ideas
Thought withdrawal and other interferences with thought	
Diffusion of thought	
Delusional perception	
Feelings, impulses and volitional acts experienced as the work or influence of others	

6.2. Current Diagnostic Criteria

The current diagnostic criteria for schizophrenia (9) require presence of two of five active-phase symptoms of delusions, hallucinations, disorganized speech, catatonic behavior, or negative symptoms for at least one month. The symptoms of schizophrenia must last for a minimum of six months and cause impairment of social and occupational functioning. Finally, one needs to rule out the presence of other diagnoses including schizoaffective disorder, bipolar disorder with psychotic features, medical or neurologic disorders or whether it is due to side effects of a medication or an illegal substance (9). A detailed account of these criteria can be reviewed in the recently published version of DSM-5 (9).

6.3. Epidemiology

Schizophrenia affects 1% of the adult population in the world (9). The point prevalence of schizophrenia is about 5/1000 population (10) and the incidence is about 0.2/1000 per year (10). This incidence rate was reported to be comparable in most societies (11); however, recent studies suggest greater variability (10). Schizophrenia has an earlier onset in males with mean ages of onset of 20 and 25 in males and females respectively (7, 10). Risk factors other than a familial history of schizophrenia include obstetric complications, parental age, prenatal infections, ethnicity, cannabis use, urbanicity and modernization (trends toward a faster-paced and more technological society) (10).

6.4. Genetics

Emerging evidence points to schizophrenia as a familial disorder with a complex mode of inheritance and variable expression (7, 12–14). While single-gene disorders like Huntington's disease have homogeneous etiologies, complex-trait disorders like schizophrenia have heterogeneous etiologies emanating from interactions between multiple genes and various environmental insults (12). Twin studies of schizophrenia suggest concordance rates of 45% for MZ twins and 14% for DZ twins (7, 15). Consistent with this, a metaanalytic study showed a heritability of 81% for schizophrenia (15). Despite this high genetic predisposition, an 11% point estimate was suggested for the effects of environmental factors on liability to schizophrenia (12, 15). Additionally, adoption studies show a lifetime prevalence of 9.4% in the adopted-away offspring of schizophrenic parents vs. 1.2% in control adoptees (16). The adoption studies also clearly show that postnatal environmental factors do not play a major role in etiology of schizophrenia (12).

The mode of transmission in schizophrenia is unknown and most likely complex and non-Mendelian (7, 12). Chromosomal abnormalities show evidence for involvement of a balanced reciprocal translocation between chromosomes 1q42 and 11q14.3, with disruption of DISC1 (disrupted in schizophrenia) and DISC2 genes on 1q42, being associated with schizophrenia (12, 17). Additionally, an association between a deletion on 22q11, schizophrenia and velocardiofacial syndrome has been reported (18). Mice with similar deletions exhibit sensorimotor gating abnormalities (19).

Linkage and association studies (12, 20, 21) show 12 chromosomal regions containing 2181 known genes (20) and 9 specific genes (12) as being involved in etiology of schizophrenia (12). Variations/polymorphisms in 9 genes including neuregulin 1 (NRG1), dystrobrevin-binding protein 1 (DTNBP1), G72 and G30, regulator of G-protein signaling (RGS4), catechol-O-methyltransferase (COMT), proline dehydrogenase (PRODH), disrupted in schizophrenia 1 and 2 (DISC 1 and DISC 2), serotonin 2A receptor (HTR2A) and dopamine 3 receptor (DRD3) have been associated with schizophrenia (Table 6.2).

More recently, genome-wide association study (GWAS) arrays have identified approximately 30 schizophrenia-associated loci including calcium channel, voltage dependent, L-type, alpha 1-C subunit (CACNA1C), serologically defined colon cancer

TABLE 6.2 Risk genes for schizophrenia.

Gene	Abbreviation	Locus
Neuregulin	NRG1	8p12-p21
Dysbindin	DTNBP1	6p22
G72	G72	13q34
D-amino acid oxidase	DAAO	12q24
RGS4	RGS4	1q21-22
Catechol-O-methyl transferase	COMT	22q11
Proline dehydrogenase	PRODH	22q11
Calcium channel, voltage dependent, L-type, alpha 1-C subunit	CACNA1C	12p13.33
Calcium channel, voltage-dependent beta 2 subunit	CACNB2	10p12.33-p12.31
N-deacetylase/N-sulfotransferse 3	NDST3	4q26-q27
Ankyrin 3	ANK3	10q21.2
Vaccinia-related kinase 2	VRK2	2p16.1
Transcription factor 4	TCF4	18q21.2
Dopamine receptor D2	DRD2	11q23.2
Metabotropic glutamate receptor 3	GRM3	7q21.11-q21.12
Ionotropic glutamate receptor AMPA 1	GRIA1	5q33.2
Ionotropic glutamate receptor NMDA subunit 2A	GRIN2A	16p13.2
Inter-alpha-trypsin inhibitor heavy chain 3	ITIH3	3p21.1
Inter-alpha-trypsin inhibitor heavy chain 4	ITIH4	3p21.1
Serologically defined colon cancer antigen 8	SDCCAG8	1q43

List compiled from (12, 22–26).

antigen 8 (SDCCAG8), inter-alpha-trypsin inhibitor heavy chain 3 and 4 (ITIH3, ITIH4), N-deacetylase/N-sulfotransferse 3 (NDST3), MIR137, ankyrin 3 (ANK3), vaccinia-related kinase 2 (VRK2), and transcription factor 4 (TCF4) (22–25). Furthermore, and very recently, a GWAS involving a large cohort of schizophrenic patients (n=36,989) compared to healthy controls (n=113,075) identified 108 loci that were associated with schizophrenia including DRD2, genes involved in glutamatergic transmission [e.g., metabotropic glutamate receptor 3 (GRM3), ionotropic glutamate receptor AMPA 1 (GRIA1), and ionotropic glutamate receptor NMDA subunit 2A (GRIN2A)]; and voltage gated calcium channels [CACNA1C, calcium channel, voltage-dependent beta 2 subunit (CACNB2)] (26).

Another means of studying the genetic basis of schizophrenia uses the technique of DNA microarray (14, 27). These studies are based on discovering genes either repressed or stimulated significantly in well-characterized postmortem brain tissues from subjects with schizophrenia and matched healthy controls; peripheral lymphocytes obtained from schizophrenic and matched healthy controls and antipsychotic-treated brains of rodents and relevant animal models of schizophrenia (Table 6.3). Genes involved in drug response, or in etiopathogenesis of schizophrenia can be compared and studied to better understand the mechanisms responsible for this illness. Lastly, a new study has reported identification of eight distinct groups of clinical entities based on genotypic networks that indicate schizophrenia is a heterogeneous group of disorders just as predicted by Bleuler nearly a century ago (258). However, this study clearly needs to be replicated further to confirm its veracity.

6.5. Etiology

The concept of schizophrenia as a neurodevelopmental disease dates back to the period of Kraepelin and Bleuler (7). Early manifestations of disease as exemplified by premorbid signs, and deficits in social interaction, were observed by Kraepelin and Bleuler (28) in children who later developed schizophrenia. Later Southard (Fig. 6.1) reported on the presence of neuropathological signs in brains of subjects with schizophrenia which further pointed to maldevelopmental origins of this disorder (29).

6.5.1. Neurochemistry of Schizophrenia

6.5.1.1. The Dopamine Hypothesis

Dopaminergic tracts are composed of four branches: 1) nigrostriatal tract, originating from the substantia nigra and ending in the dorsal striatum, deals with initiation of movement, motor control, sensorimotor coordination, cognitive integration and habituation (7, 30); 2) mesolimbic tract, originating from the ventral tegmental area and ending in hippocampus, amygdala and ventral striatum,

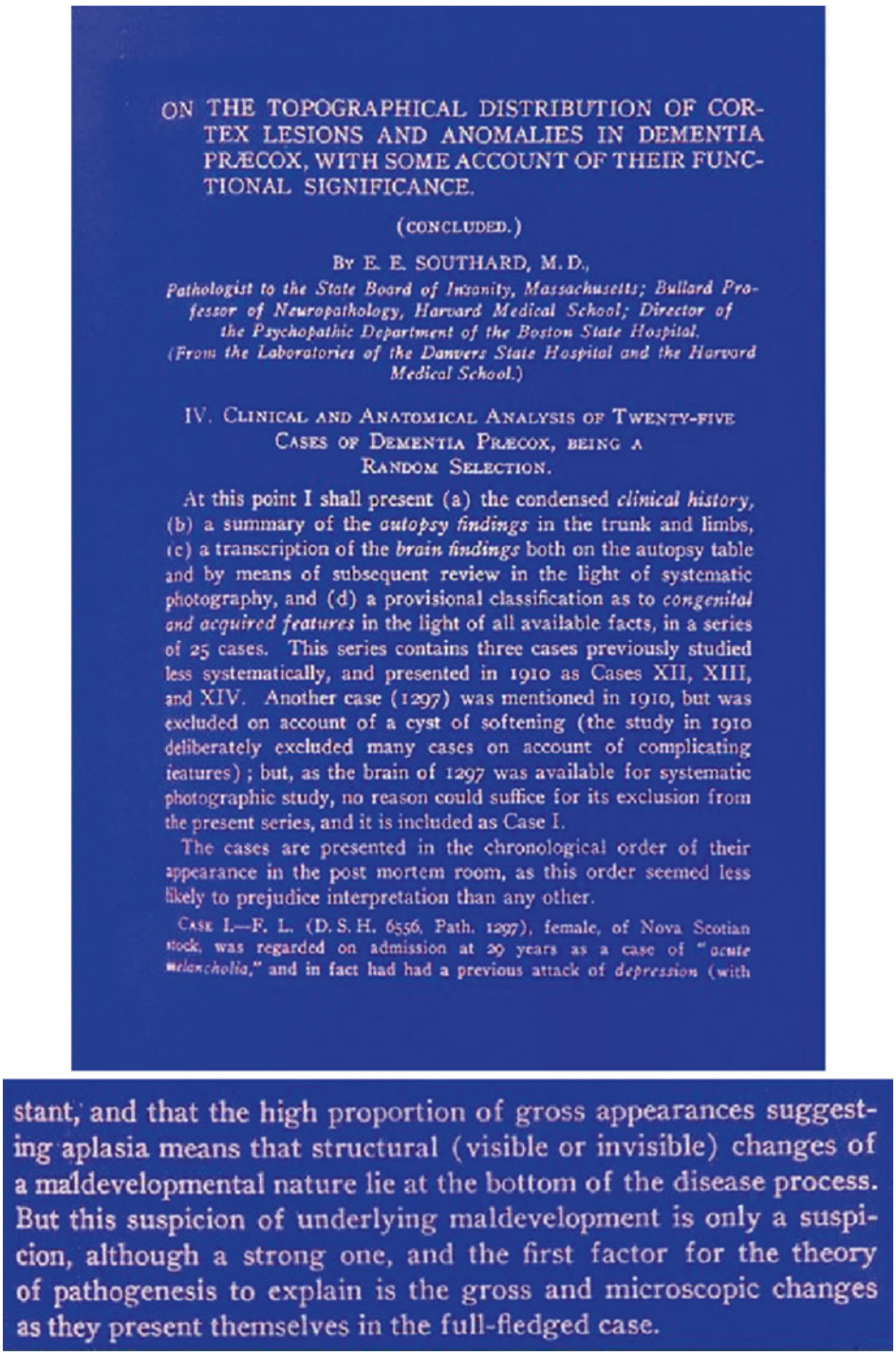
TABLE 6.3 Candidate genes: postmortem studies and animal models.

Gene	Abbreviation	Postmortem	Animal model
Adenosine A2A receptor	ADORA2A	+	+
Apolipoprotein D	APOD	+	+
CDC42 guanine nucleotide exchange factor 9	ARHGEF9	+	
Cholinergic receptor, muscarinic 1	CHRM1	+	+
Alpha7 nicotinic acetylcholine receptor	CHRNA7	+	+
Complexin 2	CPLX2	+	+
Catecholemine-O-methyltransferase	COMT	+	+
Dopamine and cAMP regulated phosphoprotein 32 kDa	DARPP-32	+	
Distal-less homeobox 1	DLX1	+	
Dopamine receptor D1	DRD1	+	
Dopamine receptor D2	DRD2	+	+
$GABA_A$ receptor, subunit alpha 1	GABRα1	+	
$GABA_A$ receptor, subunit alpha 2	GABRα2	+	
$GABA_A$ receptor, subunit alpha 5	GABRα5	+	+
$GABA_A$ receptor, subunit beta 1	GABRβ1	+	
$GABA_A$ receptor, subunit epsilon	GABRε	+	
$GABA_A$ receptor, subunit theta	GABRθ	+	
$GABA_B$ receptor 1	GABBR1	+	+
$GABA_B$ receptor 2	GABBR2	+	
Glutamic acid decarboxylase 2	GAD2	+	
Glial fibrillary acidic protein	GFAP	+	+
Glutamate receptor, ionotropic, AMPA1	GRIA1	+	
Glutamate receptor, ionotropic, AMPA2	GRIA2	+	
Myelin and lymphocyte protein	MAL	+	
Myelin basic protein	MBP	+	+
Neuronal PAS domain protein 1	NPAS1	+	+
N-deacetylase/N-sulfotransferse 3	NDST3	+	
Proteolipid protein 1	PLP1	+	
Reelin	RELN	+	+
Regulator of G protein signaling 4	RGS4	+	
Serotonin 5-HT-1A receptor	5HTR1A	+	
Serotonin 5-HT-2A receptor	5HTR2A	+	
Short stature homeobox 2	SHOX2	+	
Synapsin 2	SYN2	+	

List compiled from (14, 62–64, 115–121) and Papaleo F, Lipska BK, Weinberger DR. Mouse models of genetic effects on cognition: relevance to schizophrenia. Neuropharmacology 2012;62:1204–1220.

deals with cognitive/attentional, motivational and reward systems (7, 30); 3) mesocortical tract, originating from the ventral tegmental area and ending in the cortical structures, deals with attention, motivation and reward systems; and 4) the tuberoinfundibular tract, the cell bodies originating from the arcuate nucleus and periventricular hypothalamic areas and ending in the infundibulum and anterior pituitary, dealing with control of prolactin release (31–33). The dopamine (DA) receptors are classified into two distinct families of D1-like (D1 and D5) and D2-like (D2, D3, D4) receptors (30). The D1 receptors are localized to prefrontal cortex (PFC) and striatum. The D2 receptors are localized mostly to striatum but with lower concentrations in hippocampus, amygdala and entorhinal cortex. The D3 receptors are localized to ventral striatum. The D4 receptors are present in hippocampus and PFC. Finally the D5 receptors are found in hippocampus and entorhinal cortex (7, 30). Presynaptic DA receptors like D2 and D3 are localized to cell bodies or axon terminals of neurons (7). Dopamine helps in modulating glutamatergic inputs and pyramidal cell excitability (30).

The dopamine hypothesis of schizophrenia is based on the assumption that DA hyperactivity causes psychotic symptoms and that DA antagonists like chlorpromazine treat the psychotic symptoms (7). Additionally, administration of D-amphetamine to healthy volunteers leads to production of psychotic symptoms and worsens psychosis in schizophrenic subjects (7). One limitation of this hypothesis is that hallucinogens like LSD or psilocybin (acting on serotonin system) or dissociative anesthetics like ketamine or phencyclidine (acting on glutamate system) also cause psychotic symptoms (7, 30). A further limitation of this hypothesis is that consistent abnormalities have not been found in DA receptors or DA metabolites in subjects with schizophrenia (7, 30, 34). The two consistent postmortem findings include an increase in D2-like receptors in striatum of schizophrenics and lack of changes in striatal densities of D1 receptors or DA transporters (30). However, a recent finding of upregulated D1 receptor binding in dorsolateral PFC of schizophrenic subjects has been associated with impaired working memory performance (30).



ON THE TOPOGRAPHICAL DISTRIBUTION OF CORTEX LESIONS AND ANOMALIES IN DEMENTIA PRÆCOX, WITH SOME ACCOUNT OF THEIR FUNCTIONAL SIGNIFICANCE.

(CONCLUDED.)

By E. E. SOUTHARD, M.D.,

Pathologist to the State Board of Insanity, Massachusetts; Bullard Professor of Neuropathology, Harvard Medical School; Director of the Psychopathic Department of the Boston State Hospital.

(From the Laboratories of the Danvers State Hospital and the Harvard Medical School.)

IV. Clinical and Anatomical Analysis of Twenty-five Cases of Dementia Præcox, being a Random Selection.

At this point I shall present (a) the condensed *clinical history*, (b) a summary of the *autopsy findings* in the trunk and limbs, (c) a transcription of the *brain findings* both on the autopsy table and by means of subsequent review in the light of systematic photography, and (d) a provisional classification as to *congenital and acquired features* in the light of all available facts, in a series of 25 cases. This series contains three cases previously studied less systematically, and presented in 1910 as Cases XII, XIII, and XIV. Another case (1297) was mentioned in 1910, but was excluded on account of a cyst of softening (the study in 1910 deliberately excluded many cases on account of complicating features); but, as the brain of 1297 was available for systematic photographic study, no reason could suffice for its exclusion from the present series, and it is included as Case I.

The cases are presented in the chronological order of their appearance in the post mortem room, as this order seemed less likely to prejudice interpretation than any other.

Case I.—F. L. (D. S. H. 6556, Path. 1297), female, of Nova Scotian stock, was regarded on admission at 29 years as a case of "acute melancholia," and in fact had had a previous attack of *depression* (with

stant, and that the high proportion of gross appearances suggesting aplasia means that structural (visible or invisible) changes of a maldevelopmental nature lie at the bottom of the disease process. But this suspicion of underlying maldevelopment is only a suspicion, although a strong one, and the first factor for the theory of pathogenesis to explain is the gross and microscopic changes as they present themselves in the full-fledged case.

Figure 6.1 Article by E. E. Southard demonstrating neuropathological signs in the brains of subjects with schizophrenia being of neurodevelopmental origin.

6.5.1.2. The Serotonin Hypothesis

The serotonin (5HT) neurons emanate from the midbrain dorsal and median raphe nuclei and project to several sites including hippocampus, striatum and cortex (7, 35–37). The number of various 5HT receptor types in the brain exceed 15 with the most important receptors being 5HT1, 5HT2, 5HT3, 5HT6 and 5HT7 (7). Inhibitory somatodendritic 5HT autoreceptors (5HT1A) are localized to raphe serotonergic neurons which upon activation lead to decreased firing of the neurons (7, 38). In contrast, terminal autorecceptors modulate synthesis and release of serotonin (7). 5HT3 receptors help to stimulate dopamine release (7). Additionally, pyramidal cells in the mesocortical areas bear post-synaptic 5HT2A receptors which subserve 5HT-DA interaction in various brain areas.

While LSD and other serotonergic agonists can lead to psychotic symptoms in healthy individuals, the latter symptoms consist mostly of visual hallucinations, which are less frequently seen in schizophrenic patients. Despite the shortcomings of the serotonin hypothesis of schizophrenia, the atypical antipsychotic agents used extensively today, are potent antagonists of the 5HT2 receptors which may help in treating negative symptoms of schizophrenia and reduce extrapyramidal side effects (EPS). A recent systematic review of the literature based mostly on postmortem studies indicates significant elevation in prefrontal 5HT1A and significant reduction in 5HT2A receptors in patients with schizophrenia (39). Evidence in support of other serotonin receptors has been limited (39).

6.5.1.3. The Glutamate Hypothesis

Glutamate is the main excitatory neurotransmitter in the CNS (7, 30). Approximately 60% of neurons and 40% of synapses of the brain are glutamatergic in nature respectively (30). The glutamate receptors consist of ionotropic and metabotropic families. The ionotropic glutamate receptors (those working through Ca^{++} channels) include N-methyl-D-aspartic acid (NMDA), alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic (AMPA), and kainate receptors (5). The metabotropic family (receptors which indirectly regulate electrical signaling by activation of various second messengers) consists of groups I, II and III receptors (30). The glutamatergic hypothesis of schizophrenia is based on deceased levels of glutamate in the CSF of schizophrenic subjects (7, 31) and decreased expression of NMDA and AMPA receptors in hippocampus and thalamus of schizophrenic subjects (30, 40–43). A recent report indicates that altered glutamatergic function in the anterior cingulate is associated with more severe symptoms in subjects with schizophrenia (48). Changes in expression for various glutamate receptor types including NMDA receptors, AMPA receptors, kainate receptors, and metabotropic glutamate receptors in subjects with schizophrenia have been observed in multiple brain regions, however, a lack of consistent changes has also been noted (49). Mice with alterations in NMDA receptors, show hyperactivity and schizophrenic-like behaviors (44–47). Furthermore, altered N-glycosylation of NMDA, kainate, and AMPA receptors have been reported, suggesting that posttranslational modifications may lead to abnormal trafficking and expression of these receptors in subjects with schizophrenia (50, 51). Additionally, use of noncompetitive and competitive antagonists of NMDA receptors can lead to production of positive, negative and cognitive symptoms of schizophrenia (34). However, administration of clozapine, can block the NMDA antagonistic effects of PCP (34). Several compounds such as glycine, D-serine, and D-cycloserine have been reported to reduce positive and negative symptoms in subjects with schizophrenia (30, 34). Finally, genetic evidence also points to involvement of several genes (DAAO, G72, neuregulin, dysbindin, RGS4) which impact on glutamate system in schizophrenia (30).

6.5.1.4. The GABAergic Hypothesis

Gamma-aminobutyric acid (GABA) is the major inhibitory neurotransmitter in the mammalian brain. Postmortem evidence suggests involvement of glutamic acid decarboxylase 65 and 67 kDa proteins (GAD65 and 67), the rate limiting enzymes that convert glutamate to GABA, in the cerebellum (52, 53) of schizophrenic subjects. Supportive data (54, 55) also point to decreases in GAD67 species in brains of subjects with schizophrenia.

Investigation of GABA receptors has shown altered expression in brains from subjects with schizophrenia (60–67). $GABA_A$ receptor alpha 2 (GABRα2) and $GABA_A$ receptor epsilon (GABRε) display upregulated protein expression in lateral cerebella of subjects with schizophrenia (63, 64). Protein levels of $GABA_A$ receptor beta 1 (GABRB1) and $GABA_A$ receptor theta (GABRθ) were found to be reduced in lateral cerebella of subjects with schizophrenia (63, 64). Additionally, protein levels of GABAB receptors 1 and 2 (GABBR1 and GABBR2) were found to be significantly reduced in lateral cerebella of subjects with schizophrenia (62). In BA9, protein level of GABRθ was found to be downregulated in subjects with schizophrenia (60, 61, 64–67). These reports provide further evidence of GABAergic dysfunction in brains of subjects with schizophrenia. Lastly, Reelin, an important factor involved in synaptic plasticity which colocalizes to GABergic interneurons is reduced in brains of subjects with schizophrenia (52, 56, 57, 59) (Fig. 6.2a).

6.5.2. Neurodevelopmental Theories of Schizophrenia

The accumulation of a large body of evidence over the last century points to involvement of pathologic processes that occur in utero and lead to development of schizophrenia in adolescence (5, 68, 69). These neurodevelopmental abnormalities, beginning in utero, as early as late first or early second trimester (68, 70) have been suggested to lead to activation of pathologic neural circuits during adolescence (7) which may underlie development of psychotic symptoms in the susceptible individual.

Theodor Meynert (70) referred to frontal lobe pathology as a cause for psychosis. Later, Alzheimer reported on disorientation of pyramidal cells and neuronal loss in frontal lobes of subjects with schizophrenia (71, 72). Elmer E. Southard, an American

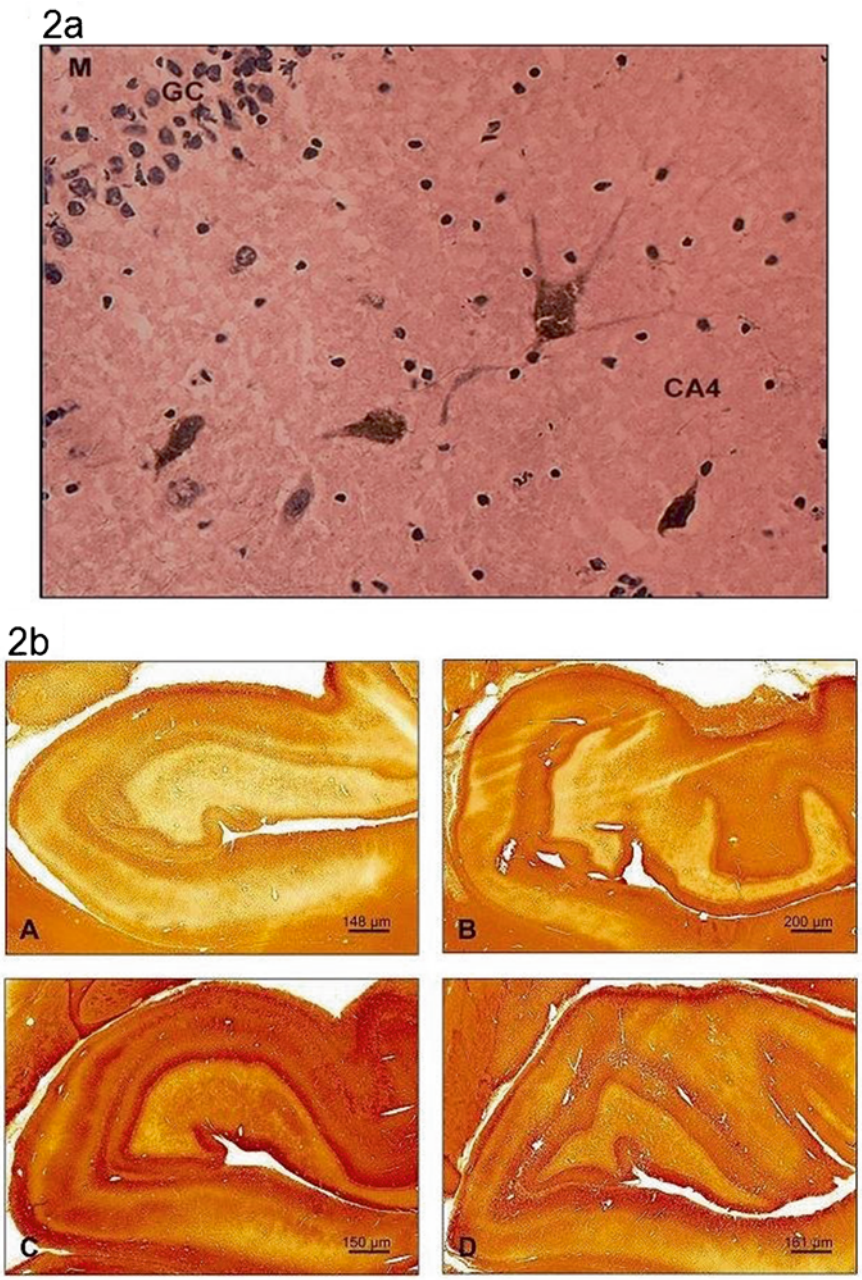


FIGURE 6.2 2a: Several Reelin-positive cells are localized to the hilus (CA4) of hippocampal complex. (M), dentate inner molecular layer, (GC), granular cell layer, 40 X magnification. 2b: SNAP-25 immunostaining is localized to various layers of ventral hippocampus in subjects with bipolar disorder (a), major depression (b) and schizophrenia (d) compared with a normal control (c). Note the diminution in SNAP-25 specific immunostaining in strata oriens and moleculare of patients with bipolar disorder (a) and schizophrenia (d) *vs* depressed (b) and control (c) subjects. 2a republished from (57), copyright (2000) with permission of Springer Science+Business Media. 2b republished from (58) (2001) with permission from Wolters Kluwer Health.

neuropathologist (73) who worked under Carl Weigert, visited Kraepelin's clinic and Franz Nissl's laboratory and produced the first convincing neuropathological study of schizophrenia (29, 73) that pointed to the maldevelopmental nature of schizophrenia. Southard also inferred that the cause for these maldevelopmental lesions may have been due to insults that interfered with brain cell growth and development (29). Resurgence of biological psychiatric research in the last four decades has strengthened Southard's pathological findings that schizophrenia is likely a neurodevelopmental brain disorder with significant genetic and environmental etiologies based on several lines of evidence which will be discussed in the following sections.

6.5.2.1. Obstetric and Perinatal Complications

There is a large body of epidemiologic research showing an increased frequency of obstetric and perinatal complications in schizophrenic patients (28). The complications observed include periventicular hemorrhages, hypoxia, and ischemic injuries (7, 74).

6.5.2.2. Brain Structural Studies

A consistent observation in schizophrenia is the enlargement of the cerebroventricular system. The abnormalities are present at onset of disease, progress very slowly, and are unrelated to the duration of illness or treatment regimen (7). Additionally, cerebroventicular enlargement distinguishes affected from unaffected discordant monozygotic twins. Furthermore, gross brain abnormalities have been identified in dorsolateral prefrontal cortex, hippocampus, cingulate cortex and superior temporal gyrus (7, 34). Some reports also indicate presence of brain structural abnormalities in individuals at high risk for development of schizophrenia and in unaffected first-degree relatives of subjects with schizophrenia (75). Additionally, studies of white matter tracts show evidence of disorganization and lack of alignment in white fiber bundles in frontal and temporoparietal brain regions in schizophrenia (76).

6.5.2.3. Histologic and Neuroimaging Studies

Numerous reports have documented the presence of various neuropathologic findings in postmortem brains of patients with schizophrenia (29, 77–80). These findings consist of cortical atrophy, ventricular enlargement, reduced volumes of hippocampus, amygdala and parahippocampal gyrus, disturbed cytoarchitecture in hippocampus, cell loss and volume reduction in thalamus, abnormal translocation of NADPH-diaphorase positive cells in frontal and hippocampal areas, reduced cell size in Purkinje cells of the cerebellum, and reduced synaptic spine density (77–79, 81). However, by far the greatest abnormalities have been found in prefrontal, ventral hippocampal and cerebellar cortices of schizophrenic brains (80). Collectively, these data reflect abnormal corticogenesis during the mid-gestation period in schizophrenic patients. Additionally, several various reports using MRI and diffusion tensor imaging (DTI) techniques have shown reduced white matter diffusion anisotropy (diffusion of water molecules in white matter) in subjects with schizophrenia (82–84). In brain white matter, water diffusion is highly anisotropic, with greater diffusion in the direction parallel to the axonal tracts. Thus, reduced anisotropy of water diffusion has been proposed to reflect compromised white matter integrity in schizophrenia (82). Furthermore, reductions in white matter anisotropy reflect disrupted white matter connections, which supports the disconnection model of schizophrenia (85). Reduced white matter diffusion anisotrophy has been observed in prefrontal, parieto-occipital, splenium of corpus callosum, arcuate and uncinate fasciculus, parahippocampal gyri and deep frontal perigenual regions of brain in schizophrenic patients (82, 86–90). There are also negative findings showing no white matter abnormalities in schizophrenia (91, 92). It is conceivable that downregulation of genes affecting production of myelin-related proteins as well as other components of axons may lay the foundation for white matter abnormalities which develop later in life in subjects who develop schizophrenia (93, 94).

Several reports indicate that glial cells are either dysfunctional (96–99) or unaffected in schizophrenia (100). Thus, absence of gliosis in brains of schizophrenic subjects may no longer imply direct support for initiation of early insults in utero in these patients (7). Furthermore, microglial activation has also been identified from several studies (101–104), suggesting dysfunctional immune activity in the brains and peripheral blood lymphocytes of subjects with schizophrenia.

6.5.2.4. Biochemical Brain Marker Anomalies and Microarray Studies of Schizophrenia

Biological markers consistent with prenatal occurrence of neurodevelopmental insults in schizophrenia include changes in the normal expression of proteins that are involved in early migration of neurons and glia, cell proliferation, axonal outgrowth, synaptogenesis and apoptosis (Table 6.4). Some of these markers have been investigated in studies of various prenatal insults in potential animal models for schizophrenia thus helping in deciphering the molecular mechanisms for genesis of schizophrenia (Table 6.3).

Multiple reports implicate various gene families as being involved in pathology of schizophrenia using microarray technology (95), i.e., genes involved in presynaptic function (95), signal transduction (94, 105–113), cell growth and migration (106), myelination (93, 94), regulation of presynaptic membrane function (107, 108), and GABAergic function (94, 109). By far the most well studied and replicated data deal with genes involved in oligodendrocyte and myelin-related functions. Hakak et al. (94) using mostly elderly schizophrenic and matched control dorsolateral prefrontal cortex homogenates showed downregulation of 5 genes whose expression is enriched in myelin-forming oligodendrocytes, which have been implicated in the formation and maintenance of myelin sheaths. Later, Tkachev et al. (93) using area 9 homogenates from Stanley Brain collection showed significant downregulation in several myelin and oligodendrocyte related genes such as proteolipid protein 1 (111), myelin

TABLE 6.4 Neurodevelopmental markers and schizophrenia.

Neurodevelopmental event	Molecule	Findings in schizophrenia
Cell migration	PSA-NCAM	↓ in dentate hilar area
	Reelin	↓ in mRNA and protein of neocortex, hippocampus and cerebellum
Synaptogenesis and axonal growth	SNAP-25	↓ in hippocampus and frontal cortex
	GAP-43	↑ in prefrontal and inferior temporal cortex; ↓ dentate gyrus
	Synaptophysin	↓ in prefrontal cortex and hippocampus
	Synapsin	↓ in hippocampus
Survival of connections	BDNF	↓ in hippocampus
Neuronal cytoskeletal proteins	MAP-2	↓ in subiculum and entorhinal cortex
	MAP-5	↓ in subiculum
Synaptic plasticity	NRG1	Nrg1 type I ↑ significantly in dorsolateral prefrontal cortex
Regulation of neurotransmitter signaling	RGS4	↓ in prefrontal cortex, motor cortex and visual cortex
Glutamatergic transmission	G72	Association of polymorphisms with early onset and male schizophrenia
	DAAO	4 intronic SNPs associated with schizophrenia in a French Canadian sample
	DTNBP1	Family association studies in Germany and Israel; DTNBP1 haplotype associated with schizophrenia in Chinese and Swedish samples
	GAD67	↓ in lateral cerebellum, PFC, and temporal neocortex
Cognition	COMT	Location in region 22q11 deleted in VCFS; variations in COMT associated with schizophrenia
Production of glutamate and GABA	PRODH	Location in region 22q11.2 deleted in VCFS; complex pattern of association with schizophrenia
	GAD1	↓ in lateral cerebellum
	GAD2	↓ in lateral cerebellum
GABAergic transmission	GABRα2	↑ in lateral cerebellum
	GABRβ1	↓ in lateral cerebellum
	GABRε	↑ in lateral cerebellum
	GABRθ	↓ in lateral cerebellum and PFC
	GABBR1	↓ in lateral cerebellum
	GABBR2	↓ in lateral cerebellum

Adapted and expanded from (7, 14, 52, 53, 56, 57, 59, 62, 63, 64, 65).

associated glycoprotein (MAG), claudin 11 (CLDN11), myelin oligodendrocyte glycoprotein (MOG), myelin basic protein (MBP), neuroregulin receptor ERBB3, transferrin, olig 1, olig 2, and Sry Box10 (SOX-10) (93).

Mirnics et al. (107) showed downregulation of genes involved in presynaptic function in the prefrontal cortex such as methylmaleimide sensitive factor, synapsin II, synaptojanin 1 and synaptotagmin 5. Another important family of genes involved in schizophrenia are genes involved in glutamate and GABAergic function. Hakak et al. (94) showed upregulation of several genes involved in GABA transmission, such as, glutamic acid decarboxylase 65 and 67 kDa protein genes. However, several reports have shown decreases in these proteins in schizophrenia (54, 112, 113). Hashimoto et al. (109) showed downregulation of Parvalbumin gene, and Vawter et al. (108) showed downregulation of glutamate receptor AMPA 2. For additional details on expression of glutamate and GABA receptors, please see Sections 6.5.1.3 and 6.5.1.4.

Another gene family of import in schizophrenia deals with signal transduction. Hakak et al. (94) showed upregulation of several postsynaptic signal transduction pathways known to be regulated by dopamine, consistent with the dopamine hypothesis of schizophrenia (110, 114) such as cAMP dependent protein kinase II-regulatory subunit and NT-related protein 2. Moreover, qRT-PCR studies have identified increased expression of dopamine and cAMP regulated phosphoprotein 32 kDa (DARPP-32), in PFC and DLPFC of subjects with schizophrenia (115, 116). Mirnics et al. (105) also showed downregulation of RGS4 gene in PFC of schizophrenia. Moreover, COMT, which degrades dopamine, shows altered expression, and is inversely correlated with expression of RGS4 (117). The cholinergic muscarinic receptor 1 (CHRM1) has been shown to be reduced in cortical and subcortical areas in brains of subjects with schizophrenia (118, 119). Furthermore, CHRNA7 mRNA expression has been shown to be reduced in blood from subjects with schizophrenia (120, 121).

6.5.2.5. Effects of Adverse Environmental Events on Brain Development In Utero

There is ample evidence to indicate that the greatest risk factor for development of schizophrenia is being related to a person with schizophrenia, i.e., in some subgroups, heredity can explain more than 80% of the liability to schizophrenia (122–124).

However, there is also a robust collection of reports indicating that environmental factors, especially viral infections, can increase the risk for development of schizophrenia (125, 126, 253, 254). Emil Kraepelin (127) referred to potential for infections causing some forms of dementia praecox (schizophrenia) during early stages of brain development. Meninger (128) described 67 cases of schizophrenia in a large cohort of patients who contracted influenza during the pandemic of 1919. Later, Hare et al. (129) and Machon et al. (130) reported on excess of schizophrenic patients being born during late winter and spring as indicators of potential influenza infections being responsible for these cases. Indeed, the majority of nearly 50 studies performed in the intervening years indicate that 5–15% excess schizophrenic births in the Northern Hemisphere occur during the months of January and March (124, 131, 132). This excess winter birth has not been shown to be due to unusual patterns of conception in mothers or to a methodological artifact (124, 133). Machon et al. (130) and Mednick et al. (134) showed that the risk of schizophrenia was increased by 50% in Finnish individuals whose mothers had been exposed to the 1957 A2 influenza during the second trimester of pregnancy. Later, nine out of fifteen studies performed replicated Mednick's findings of a positive association between prenatal influenza exposure and schizophrenia (68). These association studies showed that exposure during the 4th–7th months of gestation affords a window of opportunity for influenza virus to cause its teratogenic effects on the embryonic brain (135). Additionally, three out of five cohort and case control studies support a positive association between schizophrenia and maternal exposure to influenza prenatally (136–138). Subsequent studies have now shown that other viruses such as rubella (139) may also increase the risk for development of schizophrenia in the affected progeny of exposed mothers (124, 139). An interesting report linking viral exposure to development of schizophrenia was published by Karlsson et al. (126), who provided data suggestive of a possible role for retroviruses in the pathogenesis of schizophrenia (125). Karlsson and colleagues (126) identified nucleotide sequences homologous to retroviral polymerase genes in the cerebrospinal fluid (CSF) of 28.6% of subjects with schizophrenia of recent origin and in 5% of subjects with chronic schizophrenia. In contrast, such retroviral sequences were not found in any individuals with noninflammatory neurological illnesses or in normal subjects (124, 125). The upshot of these studies and previous epidemiological reports is that schizophrenia may represent the shared phenotype of a group of disorders whose etiopathogenesis involves the interaction between genetic influences and environmental risks, such as viruses operating on brain maturational processes (125). Moreover, identification of potential environmental risk factors, such as influenza virus or retroviruses such as endogenous retroviral-9 family and the human endogenous retrovirus-W species observed by Karlsson et al. (126), will help in targeting early interventions at repressing the expression of these transcripts. An alternate approach would be to vaccinate against influenza, thus influencing the course and outcome of schizophrenia in the susceptible individuals (125).

There are at least two mechanisms that may be responsible for transmission of viral effects from the mother to the fetus: I) Via direct viral infection. There are clinical, as well as direct experimental reports (140–143) showing that human influenza A viral infection of a pregnant mother may cause transplacental passage of viral load to the fetus. In a series of reports, Aronsson and colleagues used human influenza virus (A/WSN/33, a neurotropic strain of influenza A virus) on day 14 of pregnancy, to infect pregnant C57BL/6 mice intranasally. Viral RNA and nucleoprotein were detected in fetal brains and viral RNA persisted in the brains of exposed offspring for at least 90 days of postnatal life thus showing evidence for transplacental passage of influenza virus in mice and the persistence of viral components in the brains of progeny into young adulthood (142). Additionally, Aronsson et al. (142), have demonstrated that ten to 17 months after injection of the human influenza A virus into olfactory bulbs of TAP1 mutant mice, viral RNA encoding the nonstructural NS1 protein was detected in midbrain of the exposed mice. The product of NS1 gene is known to play a regulatory role in the host-cell metabolism (144). Several in vitro studies have also shown the ability of human influenza A virus to infect Schwann cells (145), astrocytes, microglial cells and neurons (109), and hippocampal GABergic cells (146, 147), selectively causing persistent infection of target cells in the brain. II) Via induction of cytokine production. Multiple clinical and experimental reports show the ability of human influenza infection to induce production of systemic cytokines by the maternal immune system, the placenta, or even the fetus itself (148–152). Indeed, work by Brown et al. (69) show presence of serologic evidence of maternal exposure to influenza as causing increased risk of schizophrenia in offspring (69). Offspring of mothers with elevated IgG and IgM levels, as well as antibodies to herpes simplex virus type 2 during pregnancy have an increased risk for schizophrenia. Cytokines such as Interleukin-1β, (IL-1β), IL-6 and tumor necrosis factor α (TNFα) are elevated in the pregnant mothers after maternal infection (148, 149, 152) and after infection in animal models (150, 151). All of these cytokines are known to regulate normal brain development and have been implicated in abnormal corticogenesis (153–155). Additionally, expression of mRNA's for cytokines in the CNS is developmentally regulated both in man and in mouse (156–160), emphasizing the significant role that cytokines play during neurodevelopment. IL-1β, IL-6 and TNFα cross the placenta and are synthesized by mother (161), by the placenta (162), and by the fetus (152). Maternal levels of TNFα and IL-8 have been shown to be elevated in human pregnancies in which the offspring goes on to develop schizophrenia (69, 163). A more relevant series of studies in different animal models for schizophrenia show that maternal infection with human influenza mimic poly I:C, a synthetic double stranded RNA that stimulates a cytokine response in mice, can cause abnormalities in prepulse inhibition (164), or after maternal exposure to E. coli cell wall endotoxin lipopolysaccharide, cause disruption of sensorimotor gating in the offspring (165). Finally, maternal exposure to poly I:C also causes

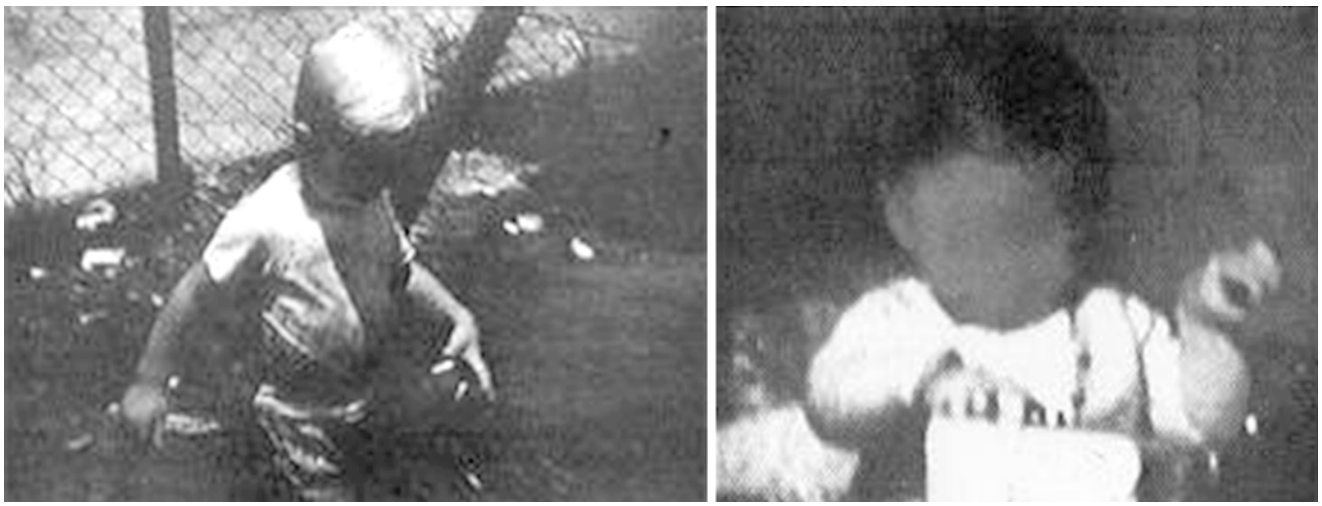


FIGURE 6.3 Abnormalities of left-hand posture in preschizophrenia children. Republished from (172), copyright (1994) with permission of Oxford University Press.

TABLE 6.5 Neurologic soft signs.

Choreoathetoid movements in preschizophrenic children
Abnormal gait
Abnormal body movements
Mannerisms
Grimacing
Stereotypies
Abnormal reflexes
Increased/decreased muscle tone
Abnormal rapid eye movements (saccades)
Frequent blinking
Dysdiadochokinesia
Astereognosis
Poor right-left discrimination
Anosognosia
Apraxia
Sympathetic arousal

disrupted latent inhibition in rat (166). All of these models suggest that direct stimulation of cytokine production by infections or immunogenic agents cause disruptions in various brain structural or behavioral indices of relevance to schizophrenia. Other factors associated with increased schizophrenic births include famine during pregnancy (124, 163) obstetric complications (167), Rh factor incompatibility (168) and autoimmunity due to infectious agents (169).

6.5.2.6. Congenital Anomalies and Developmental Dysfunction

Multiple markers of congenital anomalies indicative of neurodevelopmental insults have been found in schizophrenia (7). Such anomalies include agenesis of corpus callosum, stenosis of sylvian aqueduct, cerebral hamartomas, and cavum septum pellucidum. Presence of low-set ears, epicanthal eye folds, and wide spaces between the first and second toes, are suggestive of first trimester anomalies (7). There is, however, support for abnormal dermatoglyphics (Fig. 6.3) in patients with schizophrenia indicating a second trimester event (170). Multiple reports indicate the presence of premorbid neurologic soft signs (Table 6.5) in children who later develop schizophrenia (171, 172). Slight posturing of hands and transient choeoathetoid movements have been observed during the first two years of life in children who later developed schizophrenia (172, 173). Additionally, poor performance on tests of attention and neuromotor performance, mood and social impairment, and excessive anxiety have been reported to occur more frequently in high-risk children with a schizophrenic parent (174, 175). All of these findings are consistent with schizophrenia as a syndrome of abnormal brain development (255).

6.6. Clinical Findings

6.6.1. Clinical Signs and Symptoms of Schizophrenia

The current diagnostic criteria adopted by DSM-5 is based on extensive research dating back to initial findings of Kraepelin, Bleuler and Schneider (5, 8, 176). Unlike other medical conditions, no one sign is diagnostic of schizophrenia (7). Thus it is absolutely important to obtain as much clinical history about the patient to help establish a correct diagnosis.

As mentioned earlier, The DMS-5 criteria require presence of two or more of the following symptoms during a 1 month period: 1) delusions, 2) hallucinations, 3) disorganized speech, 4) grossly disorganized or catatonic behavior, 5) negative symptoms (flat affect, alogia or avolition). Alternatively, the diagnosis of schizophrenia may be based on presence of bizarre delusions alone, auditory hallucinations of a voice keeping a running commentary one one's daily activities, or two or more voices conversing with each other (7, 34). Delusions are fixed false beliefs not congruent with one's cultural or religious background. Schizophrenic patients may exhibit delusions that correspond to themes of persecution, grandiosity, outside control, guilt, thought broadcasting, thought withdrawal/insertion or ideas of reference (7). Bizarre delusions are highly implausible false beliefs (34). Hallucinations are abnormal perceptions of sensory experiences which occur in the absence of external stimuli. Hallucinations can be based on various types of sensory modalities such as auditory, visual, gustatory, olfactory, tactile or cenesthetic (change in the normal quality of feeling tone in a part of the body) (7, 177). Auditory hallucinations are more common in schizophrenic subjects, and occurrence of other types of hallucinations should be considered as potential signs of other medical/organic etiologies (7, 34). Command auditory hallucinations may lead the patient to act upon the command to harm self or others. Disorganized speech and behavior reflect underlying thought disorder or impairment (7, 34). Examples of abnormal speech include circumstantiality, tangentiality, derailment, illogicality, incoherence, concrete speech, clanging, neologims, echolalia, thought blocking, perseverations and poverty of content (7, 34). Disorganized behavior includes bizarre postures, stereotyped behavior, echopraxia, negativism, catatonic stupor/excitation, waxy flexibility, unprovoked outbursts of laughter or violent behavior, severe neglect of hygiene, poor self-care and grooming, grimacing, athetosis, and mutism. Grossly disorganized or catatonic behavior may also include verbigeration, primitive reflexes, autonomic hyperactivity, staring and rigidity. Finally, negative symptoms reflect deficits of normal functions and examples include affective flattening, avolition, alogia, anhedonia, social withdrawal, and diminished capacity to feel close to others (7, 34). These negative symptoms reflect endogenous markers of schizophrenia and are thus called primary negative symptoms (34). Negative symptoms such as depression or demoralization which may be due to side effects of medications, are called secondary negative symptoms.

Finally, as discussed earlier, social and occupational dysfunction, continuous presence of illness for six months and the ruling out of other illnesses or substance-related symptoms are required before a diagnosis of schizophrenia can be firmly established (9).

6.6.2. Mental Status Examination in a Subject with Schizophrenia

6.6.2.1. Appearance

Upon examination, a patient with possible diagnosis of schizophrenia may appear disheveled, exhibit evidence of poor self-care or grooming. Patient may appear suspicious, relate poorly to the examiner and exhibit bizarre postures, stereotypies, grimacing, athetosis, mutism or catatonic agitation or stupor (7). The clinician must look for presence of abnormal extra pyramidal signs (EPS) such as dystonia, tardive dyskinesia, rabbit syndrome or akathisia.

6.6.2.2. Affect

The subject may exhibit an affect which is incongruent with patient's state of mind and is described as inappropriate. Affect may also appear blunted, constricted or flat. However, absence of a sad affect does not rule out presence of a depressed mood. Flat affect may be secondary to drug induced parkinsonism or EPS.

6.6.2.3. Mood

Mood may be depressed or variable. As depression occurs frequently in schizophrenic subjects and causes a high rate of suicide, it is essential for clinicians to evaluate for presence of depression and to treat it promptly.

6.6.2.4. Speech

Evaluation of patient's speech may identify presence of loose, illogical or bizarre thought patterns. Additionally, patient may exhibit various abnormalities of speech such as tangentiality, circumstantiality, neologisms, clang association (speech directed by sound of a word rather than by its meaning) (177), perseveration and poverty of content (7). Patients may also express echolalia or thought blocking. Evidence of TD or dystonia affecting patient's speech should be investigated.

6.6.2.5. Thought Form and Content

Thought form can be ascertained while listening to patient's speech. Thus, presence of loose and illogical thought pattern is tantamount to evidence of formal thought disorder. Also, answering questions inappropriately (for example tangential responses: Q: What color is the sky? A: It rained yesterday) indicates formal thought disorder. Alternatively, thought content may be replete with evidence for delusions, ideas of reference, thought broadcasting, thought insertion or withdrawal, ideas of persecution or grandiosity or outside control. It is imperative to evaluate for presence of depression, mania, anxiety, panic, racing thoughts, irritability, suicidal and homicidal ideations or plans or past histories of suicide or violence towards others. Presence of obsessive-compulsive symptoms, past or recent histories of traumatic events and signs of PTSD should be evaluated.

6.6.2.6. Perceptual Abnormalities

Presence of hallucinations, illusions, Déja vu, depersonalization, and derealization should be determined. Intensity, frequency and past or present occurrence of various types of hallucinations should be determined. For example, specifics of gender of voices heard, loudness, origin of voices emanating from inside or outside one's head should be investigated. Presence of command auditory hallucinations which may order patient to harm himself/herself or others should be ascertained. The form and color of visual hallucinations should be evaluated. Visual hallucinations occurring during sleep, prior to or immediately after sleep are not necessarily indicative of a pathological process.

6.6.2.7. Cognition/Sensorium

Subjects with schizophrenia generally present with an intact sensorium i.e. they are alert and oriented to place, person and time. Evaluation of immediate, short and long term memory and attention should be performed. Other cognitive domains may display major abnormalities either through bedside examination or by performance of a neuropsychological battery of tests. Insight and judgement are generally evaluated by questioning patient's awareness of their illness or their ability to interact normally with others respectively. These mental abilities are more likely to be impaired in a patient with schizophrenia. Use of proverb analysis and similarities may shed light on patient's degree of abstraction or concreteness of thought. Most schizophrenic patients exhibit IQ scores 10 points lower than general public and exhibit impairments in attention, working memory, visual spatial memory, semantic memory, recall memory, and executive functions (7). Presence of cognitive abnormalities in schizophrenia appears to be independent of positive, negative or disorganization symptoms (7).

6.6.2.8. Physical Examination

As in all other fields of medicine, every psychiatrist must be able to do a focused physical examination to identify presence of any general medical or neurologic abnormalities. However, because of potential boundary issues, presence of a nurse or a chaperone in the examination room is warranted. Patients with schizophrenia have a higher burden of medical comorbidities and thus should be evaluated fully. Review of systems should cover neurologic, cardiovascular, ear, nose and throat, gastrointestinal, genitourinary, dermatologic, and endocrine systems. Presence of neurological soft signs (Table 6.5) such as abnormal gait, abnormal reflexes, changed muscle tone, abnormal rapid eye movements (saccades), frequent blinking, dysdiadochokinesia, astereognosis, poor right-left discrimination, anosognosia, apraxia, sympathetic arousal, choreoathetosis, mannerisms, grimacing, stereotypies and abnormal body movements are indicators of the neurodevelopmental origins of schizophrenia (7). Because of increased risk for diabetes and metabolic syndrome due to atypical antipsychotics, it would be judicious to obtain baseline and follow-up weight, vital signs and waist circumference (Body Mass Index) for every patient examined (178).

6.6.2.9. Neuropsychological Testing

Formal objective tests such as the Halstead-Reitan Battery, the Luria-Nebraska Battery, the Wechsler Adult Intelligence Scale, the Wechsler Intelligence Scale for Children, the Wisconsin Card Sorting Test (WCST), and the Brief Assessment of Cognition in Schizophrenia (BACS) (179) and the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) (180) can identify various brain abnormalities and should be performed in all initial evaluations.

6.6.2.10. Laboratory Investigations

6.6.2.10.1. Blood, Urine and Cerebrospinal Fluid

While no specific blood, urine or CSF tests are available to demonstrate presence of schizophrenia unequivocally, performance of certain blood and urine tests to rule out presence of nonpsychiatric causes for psychotic symptoms is warranted in all initial examinations. Tests such as thyroid function (TSH, T3, T4), RPR, HIV, fasting lipid panel, CBC with differential, metabolic panel (electrolytes, liver enzymes, BUN, glucose, creatinine) ESR, ANA, RF, B12, folate, prolactin, urinalysis, urine tox screen, blood alcohol level and baseline ECG should be performed during the initial evaluation as warranted by clinical judgment of the examining psychiatrists. Evaluation of hemoglobin A1C to rule out presence of diabetes mellitus at baseline and after institution of atypical antipsychotics is warranted. In certain cases, when suspicion of infectious etiologies is present, referral of patient to a neurologist and consultation with an infectious disease specialist for performance of a lumbar puncture is warranted.

6.6.2.10.2. Brain Imaging

Ventricular enlargement and increased brain sulcal prominence can be identified in CT or MRI views. While the findings are supportive of brain abnormality they are not specific to schizophrenia. Additionally, despite identification of a number of other brain abnormalities such as smaller cerebral and cranial size, smaller medial temporal structures (hippocampus), enlargement of lenticular nucleus, cerebellar vermal dysplasia and smaller thalamus in subjects with schizohprenia, none are diagnostic of schizophrenia (7). Shepherd et al. (181) in a meta-review of 32 publications, identified increased volumes of the ventricles and cavus septum pellucidum and reduced volumes for frontal lobe, post-central gyrus, temporal lobe, anterior cingulate, hippocampus, amygdala, thalamus, and insula in subjects with schizophrenia. Changes in volumes for fusiform gyrus, amygdala, parahippocampus, and posterior cingulate cortex/precuneus were only identified in subjects with chronic schizophrenia, suggesting an impact of the duration of illness (181).

More recently diffusion tensor imaging (DTI), has shown presence of white matter tract abnormalities in schizophrenic patients (182). While DTI abnormalities may be due to disease process itself, antipsychotic medications can impact white matter volume, cell density, and oligodendrocyte and astrocyte counts (183, 184), and thus affect DTI studies. Recent DTI studies have focused on white matter changes in drug naïve patients. These studies found white matter abnormalities in the corpus callosum (185), reduced fractional anisotropy in the left inferior longitudinal fasciculus (186), and the right superior longitudinal fasciculus II, the right fornix, the right internal capsule, and the right external capsule (187).

6.6.2.10.3. Functional Brain Imaging

Use of functional MRI (fMRI), SPECT and PET imaging has provided a wealth of information about various brain function abnormalities in schizophrenia (188–191). These abnormalities include dysfunction of information storage and retrieval by dorsolateral prefrontal cortex (DLPFC), abnormal inhibitory response to sensory stimuli by anterior cingulate cortex, abnormal encoding and retrieval of memory by hippocampus, abnormal reception and integration of sensory information by thalamic nuclei, primary sensory cortices and the multimodal cortices and impaired performance of cognitive tasks by basal ganglia, thalamus and cerebellum (34, 192–195, 203). During auditory and visual hallucinations, PET and fMRI studies have demonstrated increased activity in the auditory cortex, visual cortex, as well as the right middle temporal gyrus and/or right superior temporal cortex (196–198). Imaging during cognitive function tasks has shown altered activity in the frontal cortex of subjects with schizophrenia (199–202).

6.6.3. Differential Diagnosis

Psychotic symptoms are present in a number of conditions and must be ruled out before entertaining the diagnosis of schizophrenia.

6.6.3.1. Mood Disorders

Psychotic symptoms such as mood congruent hallucinations or delusions may occur in severe depression or mania. Acquisition of detailed history and correlative clinical data should guide the clinician as to whether these symptoms occur due to mood abnormalities. Exclusive co-occurrence of psychotic symptoms with mood symptoms should denote presence of mood disorder with psychotic features (7). Alternatively, an uninterrupted period of illness during which, at some time, there is either a major depressive episode, a manic episode, or a mixed episode concurrent with symptoms that meet criterion A for schizophrenia should point to possibility of schizoaffective disorder (9).

6.6.3.2. Psychotic Disorders Due to Medical, Neurologic or Substance-Induced Conditions

The chronology of psychotic symptoms occurring in relation to an inciting condition or in association with physical or laboratory signs indicative of a medical or neurologic disorder is helpful in distinguishing non schizophrenic psychosis. Many substances can cause psychosis such as amphetamines, substituted amphetamines such as ecstasy, hallucinogens, alcohol, barbiturates, cocaine, ketamine, PCP and belladonna alkaloids (7). Examples of medical or neurologic conditions that induce psychosis include infectious causes (herpes encephalitis, neurosyphilis, AIDS), metabolic events (acute intermittent porphyria, vitamin B12 deficiency, carbon monoxide poisoning, homocystinuria, heavy metal poisoning), neurologic events (temporal lobe epilepsy, frontal or limbic trauma, cerebrovascular accidents, Huntington's disease, metachromatic leukodystrophy, normal pressure hydrocephalus, Wernicke-Korsakoff syndrome, Wilson's disease, Jakob-Creutzfeldt's disease) and various conditions such as neoplasms, Fabry's disease, Fahr's disease, Hallervorden-Spatz disease and systemic lupus erythematosus. Clearly, obtaining historical details on clinical course, performing physical examination and doing pertinent laboratory examination will help the psychiatrist in identifying the cause of psychotic symptoms and ruling out schizophrenia (7).

6.6.3.3. Other Psychotic Disorders

Psychotic symptoms may occur during a period of mood abnormality such as depression, mania or mixed episode with mood symptoms present for a substantial portion of the total period of illness denoting schizoaffective disorder. In brief psychotic disorder, schizophrenic symptoms occur for at least 1 day but less than 4 weeks and these may occur in presence or absence of a marked stressor or with onset within 4 weeks postpartum (9). In schizophreniform disorder, prodromal, residual or active schizophrenic symptoms occur for at least 1 month but less than six months in duration. Delusional disorder refers to nonbizarre delusions in the absence of hallucinations, disorganized speech or behavior or negative symptoms or mood disorder. Finally, psychotic disorder not otherwise specified deals with disorders that do not meet the criteria for any of the above-mentioned diseases and for which adequate information is not available.

6.6.3.4. Other Axis I Disorders

Symptoms which may resemble hallucinations or paranoia may be observed in PTSD patients but these ensue following a traumatic event. Severe intrusive thoughts in OCD patients neither reach the level of delusionality seen in schizophrenia or if they occur in absence of insight do not accompany functional incapacity seen in psychotic patients. Finally, in subjects with hypochondriasis or body dysmorphic disorder no hallucinations or delusions are present (34).

6.6.3.5. Personality Disorders

Symptoms of schizotypal, schizoid, paranoid, and borderline personality disorders lack an exact onset of disease, are present throughout patient's life and are mild (7). However, these do not reach a level meeting criterion A for schizophrenia, and do develop as early as adolescence or early adulthood.

6.7. Pharmacological Treatments of Schizophrenia

6.7.1. Clozapine

Clozapine is a dibenzodiazepine and the prototype for most of atypical antipsychotics [agents which may treat positive, negative or cognitive symptoms of schizophrenia, have decreased liability for EPS and tardive dyskinesia, may be effective for a proportion of treatment nonresponsive patients and exhibit greater 5HT2 over D2 receptor antagonism and do not cause hyperprolactinema

(204, 205)]. It has a complex pharmacologic profile encompassing affinities for 5HT2A, 5HT2C, 5HT6, 5HT7, α1, α2 adrenergic, M1 muscarinic and histaminergic receptors (7). Clozapine exhibits inverse agonist activity at 5H2A and 5HT2C receptors blocking constitutive activity of these receptors (34). The ratio of 5HT2A to D2 receptor affinities may signal clozapine's low EPS profile (7).

Clozapine has been shown to be effective in treatment resistant schizophrenia (206). This important study compared the efficacy of clozapine to chlorpromazine in 268 subjects with treatment resistant schizophrenia (defined as having failed to respond to at least three prior antipsychotics). By 6 weeks, 30% of the clozapine-treated group but only 4% of the chlorpromazine-treated group responded to the respective medications (206, 17). Thus, clozapine remains the only antipsychotic agent to date that is FDA-approved for treatment-resistant schizophrenia (206). Additionally, other studies have shown superiority of clozapine vs. typical agents in treatment of total psychopathology, EPS and TD and categorical response to treatment (206). Clozapine reduces positive, negative and cognitive symptoms of schizophrenia without causation of EPS, TD or hyperprolactinemia (34). Furthermore, clozapine has been shown to reduce depression and suicidality (7, 34).

The dose range of clozapine varies from 150–450 mg/day for most patients (259). The initial dose of 25 mg/day must be titrated upwards slowly (increments of 25 mg/3 days) due to hypotensive and tachycardic side effects (7). The average dose is about 400–500 mg/day as a twice daily regimen (7). Plasma levels of 350–400 ng/ml have been associated with good clinical response (7, 256).

Despite clozapine's important clinical efficacy, several side effects must be considered as potentially significant and life threatening. Agranulocytosis occurs within the initial 4–18 weeks of treatment, necessiting monitoring of while blood cell (WBC) and neutrophil count every week, for the first 6 months (34), every 2 weeks for the next 6 months and once monthly thereafter (7). If the WBC count falls below 3000 cells per mm^3 or the absolute neutrophil count below 1500 cells per mm^3, clozapine administration must be stopped. Upon diagnosis of agranulocytosis, administration of granulocyte colony stimulating factor (G-CSF) and hospitalization, is warranted. The death rate from agranulocytosis is ≈ 1 per 10,000 patients (34). Other side effects of clozapine include sedation, weight gain, seizures, OCD symptoms, hypersalivation, tachycardia, hypotension, hypertension, stuttering, neuroleptic malignant syndrome, urinary incontinence, myocarditis, constipation, hyperglycemia, eosinophilia and fever (7). Seizures can be treated with valproic acid or lamotrigine supplementation (207–209).

6.7.2. Risperidone

Risperidone is a member of the benzisoxazole family of atypical agents and the second FDA approved antipsychotic agent classified as atypical to be marketed in USA. Several studies suggest that risperidone may be more effective than typical antipsychotics in acute and maintenance treatment of schizophrenic subjects (207). While risperidone may be superior to typical agents in treatment-resistant patients, it is not considered as effective as clozapine in this vulnerable group of schizophrenic patients (210).

The recommended dosage of risperidone is 2–8 mg/day (9). Risperidone causes higher occupancy of D2 receptors than does clozapine and may cause mild EPS even at 2–4 mg/day dosage range (7). Additionally, risperidone causes hyperprolactinemia. Other side effects include akathisia, weight gain, sexual dysfunction, decreased libido and galactorrhea (7). Risperidone is available in depot form for injection.

6.7.3. Olanzapine

Olanzapine is a thienobenzodiazepine agent and the third FDA approved atypical agent marketed in the USA in late 1990's. This novel agent exhibits nanomolar affinity at several receptor sites including D1–D4, 5HT2, 3, 6, muscarinic M1–5, α1 adrenergic and H1 histaminergic sites (7). Additional novel findings show that olanzapine causes modulation of several important brain genes like Reelin, insulin, regulator of G-protein signaling (RGS2), pyruvate kinase, calbinden and homer 1 after chronic administration in rats (211). Furthermore, olanzapine was shown to increase glucogenesis in brain via multiple pathways potentially linking its ability to produce glucose for energy consumption in brain to its metabolic side effect profile in the treated subjects (212). Olanzapine also downregulates the soluble isoform of COMT in frontal cortex of rats helping in upregulating the levels of dopamine in this important brain area (213).

Olanzapine has several characteristics of an atypical agent such as low EPS propensity, chemical structural similarity to clozapine, lack of hyperprolactinemic side effect, broad efficacy and ability to treat negative symptoms of schizophrenia (7). Multiple studies have shown olanzapine to have some efficacy over typical agents in the acute and maintenance treatment of schizophrenia (210) and in treatment of refractory patients. The dose range for olanzapine is 5–20 mg/day (259). Despite olanzapine's beneficial effects, several side effects including weight gain, metabolic disturbances, sedation, dizziness and transient liver transaminase elevations should be watched for (7).

6.7.4. Quetiapine

Quetiapine is a member of dibenzothiazepine family of atypical agents with high affinity for 5HT2A, α1 adrenergic and H1 histaminergic receptors (7). Quetiapine also exhibits moderate affinity for D2 and low affinity for M1 muscarinic receptors (7). Quetiapine dose range is 300–600 mg/day with similar efficacy as typical agents and is associated with low EPS propensity and prolactin elevation (207). The most common side effects include sedation, dry mouth, agitation, constipation and orthostatic hypotension (7). Quetiapine can cause QT prolongation (257) and has the potential to cause torsade de pointes and has a warning label based on FDA recommendations.

6.7.5. Ziprasidone

Ziprasidone is a benzothiazolyl piperazine with high affinity for serotonergic (5HT1A, 5HT2A, 5HT2C, 5HT1D) and dopaminergic (more D3, less D2) receptors. It has weak affinities for muscarinic and histaminergic receptors (7). Recent data indicate that ziprasidone has similar antipsychotic efficacy to haloperidol, is associated with minimal weight gain, sedation or prolactin elevation (207). The dose range is 80–160 mg/day. Despite initial concerns for ziprasidone causing QT-interval changes, such as torsade de pointes, FDA does not require ECG acquisition prior to treatment and no published reports indicate any cardiotoxic effects (207).

6.7.6. Aripiprazole

Aripiprazole is the first FDA approved partial dopamine D2 agonist, marketed in 2002, with partial agonist activity at 5HT1A receptor and 5HT2A antagonism (34, 207). Aripiprazole has low EPS propensity, low liability for hyperprolactinemia and weight gain (207). The dose range is 10–20 mg/day (34). Aripiprazole is effective in short and long term treatment of schizophrenia (207). Side effects may include activation and nausea (34).

6.7.7. Paliperidone

Paliperidone was approved for the treatment of schizophrenia in 2006 and schizoaffective disorder in 2009 (214). Paliperidone, a metabolite of risperidone (9-hydroxyrisperidone), is a dopamine D2 receptor antagonist (215). The approved range of doses for paliperidone is 6–12 mg/day (216–219, 259). Clinical data from short-term treatment trials of paliperidone have demonstrated superior efficacy to placebo on several psychometric tests (216–218). Results from a long-term study also found that paliperidone was superior to placebo in preventing relapse [25% for paliperidone vs. 53% of placebo (220)]. Pooled data from three 52-week studies found that paliperidone treatment resulted in maintenance of clinical improvements and was well-tolerated (221). Meltzer et al. (219) using data from three six week studies (216–218) found that subjects treated with paliperidone showed no significant differences in weight gain or for a number of metabolic measurements including fasting glucose, triglycerides, lipoproteins, or cholesterol levels when compared with controls.

6.7.8. Iloperidone

Iloperidone was approved for the treatment of schizophrenia in 2009. Unlike other antipsychotic medications, iloperidone has relatively high affinity for noradrenergic alpha 1 receptors rather than serotonin 5HT2A and dopamine D2 receptors (222). Iloperidone needs to be titrated to its target dose of 12–24 mg/day, and is generally administered twice daily (222). There have been four short-term double-blind, placebo- and active controlled studies of iloperidone's efficacy (223–225). A meta-analysis of pooled patient data found that iloperidone was significantly more effective than placebo in reducing PANSS total score, PANSS positive subscale, PANSS negative subscale, and BPRS-derived total scores (226). Data from three, pooled long-term studies of iloperidone vs. haloperidol found that iloperidone had similar efficacy as haloperidol and a favorable long-term safety profile (227). More recently, Cutler et al. (228) similarly found that iloperidone was safe and tolerable long-term with regard to weight gain and metabolism, however, there was no improvement in total PANSS scores over baseline. Iloperidone is known to increase corrected QT interval (QTc), however, there have not been any reports of serious cardiac dysfunction associated with increased QTc (229).

6.7.9. Asenapine

Asenapine was approved for use in 2009 and is used for the treatment of schizophrenia and for acute treatment of manic or mixed episodes of bipolar I disorder (222). Asenapine is absorbed through the oral mucosa as its bioavailability is less than 2%

if swallowed (230–232). Asenapine has high affinity for multiple serotonin receptors (5-HT2A, 5-HT2B, 5-HT2C, 5-HT6, 5-HT7) and the dopamine D3 receptor (222). Asenapine does not need to be titrated and is dosed at 5 mg/day bid for acute schizophrenia and 10 mg/day bid for maintenance (222). A meta-analysis of four short-term studies of asenapine's efficacy (230, 233, 234) found that asenapine was more effective than placebo with regard to change in PANSS total score (235). Longer-term studies employing olanzapine as an active control found that olanzapine was more effective than asenapine in reducing PANSS scores at the end of 52 weeks (236) and the 16 item negative system assessment (NSA-16) at the end of 26 weeks (237). However, Buchanan et al. (237) found that during the extension study, that asenapine was superior to olanzapine in changing NSA-16 scores at 52 weeks. When compared with placebo, asenapine does not appear to have any effect on weight gain, fasting serum glucose, total cholesterol, or triglyceride levels (230, 238).

6.7.10. Lurasidone

Lurasidone was approved for use in 2010 and is used to treat schizophrenia and depressive episodes associated with bipolar I disorder (222). Lurasidone is a full D2 dopamine and 5-HT2A receptor antagonist (222). Unlike iloperidone or asenapine, lurasidone is taken once a day and has a target dose of 40–80 mg/day for the treatment of schizophrenia (222, 259). A number of short-term, six-week trials have shown that lurasidone, at a variety of doses, is superior to placebo for the treatment of acute schizophrenia as determined by reduction in PANSS scores (239–243). A long term extension by Loebel et al. (244) found that lurasidone produced higher rates of remission than quetiapine. A second long-term study found improvement in mean PANSS total scores, mean Clinical Global Impression Schizophrenia (CGI-S) score, and mean Calgary Depression Scale for Schizophrenia (CDSS) score (245). Lurasidone does not appear to cause increased weight or changes in metabolic values, nor does it impact QT interval (222).

6.7.11. Typical Antipsychotics

Results of CATIE trials (210) have indicated that there may not be significant differences between several atypical agents (clozapine, olanzapine, ziprasidone, aripiprazole and risperidone) and a typical agent (perphenazine) with regards to efficacy in treatment of schizophrenic positive symptoms. Indeed, introduction of chlorpromazine and later antipsychotic agents like haloperidol in the 1950's revolutionized the treatment of schizophrenia (7). These agents clearly treated positive symptoms in 60–70% of patients and enabled many patients to leave hospitals for the first time in decades. The early hypotheses suggested that action of typical antipsychotics in ameliorating the positive symptoms of schizophrenia were due to their dopaminergic antagonism (7). Recent genetic and microarray studies have revealed that most if not all antipsychotic agents probably treat schizophrenic symptoms by modulating a large number of brain genes whose upregulation or repression chronically, may lead to stabilization of positive, negative and cognitive deficits in schizophrenia (246–248). Thus, it appears that modulation of major neurotransmitters like dopamine, serotonin, glutamate, GABA and acetylcholine by various antipsychotic agents may only be part of a larger array of brain genes and proteins that may be involved in treatment of schizophrenia.

6.7.12. Multiple Phases of Pharmacologic Treatment

In acute phase treatment, patients with florid psychotic symptoms are generally admitted to a hospital setting and given short acting antipsychotic agents (ziproasidone, olanzapine or haloperidol) alone or in combination with benzodiazepines and/or anticholingerics. The clinical decision to begin antipsychotic treatment is dependent on several factors including side effect profile, past history of response to medications and patient preference (Table 6.6). The order of antipsychotic agents of choice based on decreased propensity for metabolic side effects/EPS/TD may be aripiprazole, quetiapine, risperidone/paliperidone, ziprasidone, olanzapine, haloperidol. In cases of noncompliance, depot medications such as long acting risperidone, haloperidol or fluphenazine may be administered (34).

In continuation phase treatment, patient's response to antipsychotic agent, side effect profile, tolerability and compliance will be monitored carefully (34). It is generally expected to achieve optimal response to most agents by 4–6 weeks, however, longer periods of therapy may be necessary in certain individuals. In some patients, residual constellation of positive, negative or cognitive symptoms may remain. In some cases, one antipsychotic agent may be switched with another medication. Alternatively and specifically in treatment nonresponsive patients, clozapine alone or in combination with other agents such as valproate, benzodiazepines, antidepressants or lithium may be necessary to treat various symptoms.

Table 6.6 Commonly used antipsychotic drugs.

Class and drug name	Dosage range (mg)	Clorpromazine equivalents (mg/day)	Parenteral dosage (mg)	Galenic forms
Typical drugs				
Chlorpromazine	200–600	100	25–75	O, L, I, S
Fluphenazine	2–20	2.5	5–10	O, L, I
Fluphenazine decanoate	–	–	25–50 every 1–4 weeks	–
Fluphenazine enanthate	–	–	25–50 every 1–4 weeks	–
Haloperidol	4–20	2.5	5–10	O, L, I
Haloperidol decanoate	–	–	50–150 every 1–4 weeks	–
Loxapine*	60–100	10	25–50	O, L, I, OH
Mesoridazine	75–300	83	25–50	O, L, I
Molindone	30–100	10	NA	O, L
Perphenazine	8–32	8	6–12	O, L, I
Pimozide	2–6	1	NA	O
Thioridazine	150–600	100	NA	O, L
Thiothixene	5–30	5	2–4	O, L, I
Trifluoperazine	5–20	5	4–9	O, L, I
Atypical drugs				
Aripiprazole	10–20	7	NA	O, L, I
Asenapine	10–20	5	NA	OD
Clozapine	150–450	67	NA	O
Iloperidone	12–24	6	NA	O
Lurasidone	40–80	20	NA	O
Olanzapine	5–20	5	10–15	O, I, OD
Paliperidone	6–12	2	234 mg on day 1; 156 mg one week later; and 117 mg monthly for maintenance	O, I
Quetiapine	300–600	167	NA	O
Risperidone	6–8	1.3	NA	O, L, I, OD
Risperidone microspheres	–	–	25–50 every 2 weeks	I
Ziprasidone	80–160	40	20–40	O, L, I

O, oral; L, liquid; I, Injection; OH, oral inhalation; S, suppository. OD, oral disintegrating form.
*Loxapine is now FDA approved as the first inhalational-based antipsychotic.
Baldessarini RJ. Chemotherapy in Psychiatry. Pharmacologic Basis of Treatments for Mental Illness, 3rd edition. New York, Springer;2013.
Gardner DM, Murphy AL, O'Donnell H, Centorrino F, Baldessarini RJ. International consensus study of antipsychotic dosing. Am J Psychiatry 2010;167:686–693.

In maintenance phase treatment, patients who have responded well to various agents should be treated indefinitely to prevent relapse and worsening of disease process. In treatment refractory cases, clozapine appears to be the only drug with proven efficacy (34).

6.8. Antipsychotic Related Side Effects

One of the major reasons for choice of new second generation antipsychotics relates to high frequency of several side effects which are more prevalent with typical agents. For example, extrapyramidal side effects (EPS) such as dystonias (repetitive involuntary skeletal muscle contractions, (Fig. 6.4), dyskinesias [slow or tardive dyskinesias (TD) or severe involuntary choreiform, athetoid, or rhythmic muscular contractions which may involve face, neck, tongue, hands, trunk, legs], pseudoparkinsonism, rabbit syndrome, akathesias occur secondary to use of high potency typical antipsychotics. All of these side effects except for TD can be treated by judicious use of anticholinergics, benzodiazepines or propranolol or reduction in dose of antipsychotic agents or by changing to an atypical agent. There are no proven treatments for TD. Non-neurologic side effects may include hyperprolactinemia, gynecomastia, impotence, amenorrhea, weight gain, hematologic effects, jaundice and cardiac effects (7).

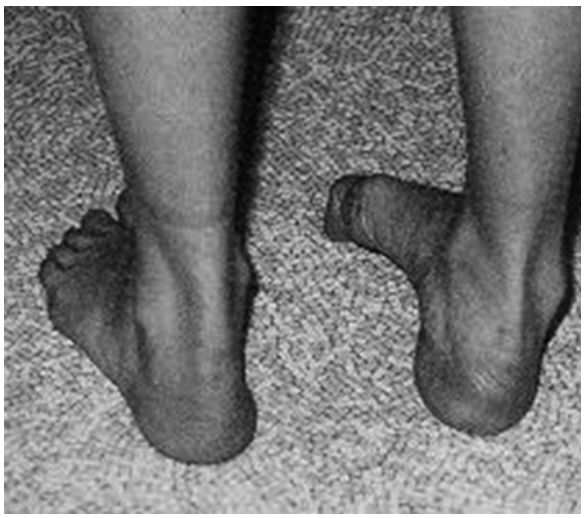


FIGURE 6.4 Foot dystonia, which is most obvious when the patient attempts to walk. Republished with permission of Taylor and Francis Group LLC Books from Uiti RJ, Francois G, Vingerhoets G, Tsui JKC, Limb Dystonia, in: Handbook of Dystonia, King J, Tsui JKC eds. copyright (1995); permission conveyed through Copyright Clearance Center, Inc.

6.9. Electroconvulsive Treatment of Schizophrenia

ECT treatment (6–12 treatments) may be an adjunct in treatment-refractory patients and when required in rapid control of excited catatonia and severe agitation. Long term use of ECT in treatment of schizophrenia is not supported by current literature (7).

6.10. Psychosocial Treatment

There are several psychosocial treatment modalities like cognitive-behavioral therapy, personal therapy, compliance therapy, acceptance and commitment therapy as well as supportive psychotherapy which have been found to help patients and their families to deal with the disease process, noncompliance issues and improvement of patients' living and work functioning (34). Application of case management, token economy, reduction of expressed emotion by patients' family and assertive community treatment, social skills training and cognitive rehabilitation strategies can all help patients with schizophrenia to have a better outlook on life and to improve their compliance with medication regimen (34).

6.11. Time Course of Schizophrenia

Disease onset is quite variable. The prodromal phase consists of a period during which patient may experience social withdrawal, decreased motivation, poor cognition, increasing odd behavior and restricted affective range (34). During the active phase (first psychotic break), patient exhibits florid psychotic symptoms either in response to life stressors or following substance abuse (34). In residual phase, there remains some schizophrenic symptoms which persist despite treatment.

6.12. Prognosis and Course of Illness

The modern concept of the prognosis of schizophrenia is based on multiple outcome measures. Four types of outcome measures have been identified: psychopathology, work function, social function, and rehospitalization. These measures could vary independently in schizophrenia, and although they are central to evaluating outcome in schizophrenia, other measures such as cognitive function, general health, and suicide are also important.

Outcome in schizophrenia can be predicted partially by age at onset and by the nature of the prodrome and first episode (Table 6.7). Early age at onset (e.g., 14–18 years) is often associated with a worse outcome than is later age at onset. An insidious rather than an abrupt onset is also associated with a poor outcome. If the initial clinical presentation is characterized mainly by negative symptoms, outcome is likely to be poor, both in the short and long term. Conversely, florid psychosis and an abrupt onset are both likely to be associated with a good prognosis because antipsychotic drugs are much more effective against positive symptoms and disorganization than they are against negative symptoms and cognitive disturbance.

TABLE 6.7 Predictors of course and outcome in schizophrenia.

Factor	Good outcome	Poor outcome
Age at onset[1]	About 20–25	Below 20
CT/MRI studies[1]	Normal morphology	Dilated ventricles, brain atrophy
Initial clinical symptoms[1,2]	Catatonia, paranoia, depression, schizoaffective diagnosis, atypical symptoms, confusion	Negative symptoms (e.g., flat affect, poverty of thought, apathy, asociality); obsessive-compulsive symptoms
Occupational record[1]	Stable	Irregular
Onset[1]	Acute, late	Insidious
Rate of progression[1]	Rapid	Slow
Sex[1]	Possibly females	Possibly males
Length of episode prior to assessment[2]	Months or less	Years
Being in a developing country[3]	Present	Absent
Cannabis use[3]	Absent	Present
Optimal prenatal care[3]	Present	Absent
Precipitating factors[3]	Present	Absent
Socioeconomic status[3]	Middle, high	Low
Substance abuse[3]	Absent	Present
Stressful life[3]	Absent	Present
Early treatment with medications[4]	Present	Absent
Long term drug maintenance[4]	Present	Absent
Response to medications initially[4]	Present	Absent
Family history of mental illness[5]	Affective	Schizophrenia
Other adverse social factors[5]	Absent	Present
Prenatal adverse events[5]	None	Present
Presence of certain gene polymorphism e.g., COMT. NMDA2A[5]	Absent	Present

1 = Clinical; 2 = Diagnosis; 3 = Environment; 4 = Treatment; 5 = Genetic; adapted from Meltzer et al. 2008 (218); Perkins et al. 2006 (249).

Results from several long term reports studying outcome in schizophrenia show that over a 15 year period several disease courses may emerge: 1) 9–38% of patients will have a sustained recovery (249); 2) 10% of the patients will have a persistent unremitting course (249–252); 3) 67% of patients will have a good outcome (249, 250); 4) 32% of patients will have a poor outcome (249, 250); and 5) 10% will die by suicide (249). Generally, the overall prognosis of schizophrenia is more favorable now than before neuroleptics were introduced, mostly because of improvements in pharmacologic therapies and, to some degree, changes in psychosocial treatment strategies. The increased mortality in patients with schizophrenia today is the result of suicide, accidents, and diseases (e.g., infections, type II diabetes, heart disease, and in females, breast cancer) (249).

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7
Schizoaffective and Schizophreniform Disorders

William Coryell, M.D.

Abstract The term "Schizoaffective Disorder" has been variously defined but has been generally applied to individuals in whom features of schizophrenia and a mood disorder coexist. Studies of phenomenology, clinical course, and heritability, have, when taken together, yielded results consistent with the view that a majority of individuals who meet criteria for schizoaffective disorder, in fact, have either schizophrenia or a mood disorder with psychotic features and that a minority suffer from a geneotypic concurrence of both illnesses. The treatment of individuals with schizoaffective disorder should initially assume the presence of a psychotic mood disorder, however.

Keywords Schizoaffective · Schizophrenia · Mood disorder · Family study · Follow-up study

7.1. Definition

Nosological ambiguity is a well-recognized impediment to progress in psychiatry and has been particularly so for the concept of schizoaffective disorder. This is due in part to the conceptual difficulty inherent in any intermediate or boundary category and in part to a series of shifts in the term's definition since operational criteria were introduced.

The Research Diagnostic Criteria (RDC) (1) provided the first definition that was both widely used and operational. These relatively inclusive criteria differed according to whether a manic or depressive syndrome was present but, in essence, required a full affective syndrome accompanied either by Schneiderian first-rank symptoms, by a history of mood-incongruent psychotic features "in the absence of" or "to the relative exclusion of" affective symptoms or by a history of delusions or hallucinations at a time when prominent manic or depressive symptoms were absent. The RDC definition has been used in more studies of schizoaffective disorder than any other single, definition. Yet it was supplanted, at least in the official American nomenclature, when the DSM-III assigned this term to a residual category for those who did not meet criteria for schizophrenia or a mood disorder but who appeared to have features of both. Moreover, the boundaries for major mood disorders were expanded so that many patients with RDC schizoaffective disorder met criteria in the DSM-III for major depression or mania with mood-incongruent psychotic features (2). The DSM-III-R provided operational criteria for the term but applied it only to patients who had had delusions or hallucinations without "prominent mood symptoms" for at least 2 weeks in the index episode. This definition survived largely intact in DSM-IV. The DSM-5 was modified to clarify the distinction between schizoaffective disorder and schizophrenia with the requirement that a major mood syndrome has been present for the majority of the total duration of the active and residual portions of the illness.

These circumstances recommend a generic use of the term *schizoaffective disorder* in any broad overview of the topic. Thus, the following will apply the term to any condition in which there is a coincidence of schizophrenic and affective symptoms or in which there is the occurrence of an affective syndrome at one point and a schizophrenic syndrome at another. At the same time, the full interpretation of any particular study's results requires attention to the definition of schizoaffective disorder used.

W. Coryell, M.D. (✉)
George Winokur Professor of Psychiatry, Department of Psychiatry, University of Iowa Carver College of Medicine, Iowa City, IA, USA
e-mail: william-coryell@uiowa.edu

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7.2. Etiology

Many medical conditions can produce symptoms that suggest schizoaffective disorder. Identification of a cause, however, precludes the diagnosis and, in the DSM-5, the diagnosis becomes one of a psychotic or mood disorder "due to the effects of a substance or another medical condition." The etiology of schizoaffective disorder is, by definition, unknown.

The question then becomes, does schizoaffective disorder share its unknown etiology with schizophrenia, with affective disorder, with both, or with neither? Or does schizoaffective disorder simply label a genotypically mixed group made up partly of mood disorder patients and partly of schizophrenic patients? Because both schizophrenia and the mood disorders are heritable, family studies offer one approach to weighing these alternatives. The relevant hypotheses can be tested in the following ways: (1) if schizoaffective disorder is simply a variant of affective disorder (3, 4), then schizoaffective probands will have no more familial loading for schizophrenia than do mood disorder probands; (2) if schizoaffective probands simply have a variant of schizophrenia, as is implied by the listing of schizoaffective disorder under schizophrenia spectrum disorders in both ICD-10 and DSM-5, their families will contain no more mood disorder than the families of schizophrenic probands; (3) if schizophrenia, schizoaffective disorder, and mood disorder all share a common etiology and form a spectrum, patients in any of these three categories will have relatives at increased risk for disorders in the other two categories; and (4) if schizoaffective disorder is a separate disorder, the first and second predictions listed above should apply and the families of schizoaffective probands will be loaded for schizoaffective disorder, provided this condition is, likewise, familial.

Table 7.1 summarizes informative studies published in English over the past 40 years. Because schizophrenia-like symptoms may have different implications when they coexist with depressive syndromes than when they coexist with manic ones (5–8), this review summarizes these studies in three groups: those that isolated probands with schizoaffective mania, those that isolated probands with schizoaffective depression, and those that did neither. This display serves to reveal overall patterns in group relationships. Many pairwise comparisons were statistically significant, but this information is omitted because statistical significance depends on sample sizes and these varied greatly across studies. For studies using DSM-III and DSM-IIIR systems, the schizoaffective proband group is comprised of patients who met the corresponding criteria for major depression or mania with mood-incongruent psychotic features or, more rarely, for schizoaffective disorder. The mood disorder proband groups consist of those with mood disorder with or without mood-congruent psychotic features.

Those studies that did not separate schizoaffective manic patients from schizoaffective depressed patients consistently failed to support the first hypothesis. In 11 of 11 studies, relatives of schizoaffective probands were more likely to have schizophrenia than were relatives of mood disorder probands. The same was true in 5 of the 6 studies that considered schizoaffective depression apart. Some earlier reports concerning schizoaffective mania supported the first hypothesis (4, 20, 21, 30), but later ones (16, 23, 31) showed patterns in line with those found in studies of schizoaffective depression.

Of those that included schizophrenia cohorts for comparison, all fourteen reported higher rates of mood disorder in the families of schizoaffective probands than in the families of schizophrenic probands. Thus the second of the hypotheses—that schizoaffective disorder is altogether a variant of schizophrenia—can be rejected.

The consistency with which schizophrenia was overrepresented in the families of schizophrenia probands, together with the regular predominance of mood disorder in the families of mood disorder probands, argues against a spectrum hypothesis. Moreover, those few studies which have included normal control probands have generally shown no increase in mood disorder within families of schizophrenic probands (28, 29, 32) nor any increase in schizophrenia within the families of mood disorder probands (28, 29, 32).

Studies of twins and of sib-pairs offer another way to investigate schizoaffective disorder. If most schizoaffective cases result from a "third psychosis" there should be few affected twins or sib-pairs in which one member has schizoaffective and the other has schizophrenia or mood disorder. An early study, in fact, did find a 100% concordance for schizoaffective disorder (33). The same raters assessed members of both twin- pairs, though, and were, therefore, subject to bias. In contrast, Tsuang (34) conducted blind assessments of sib-pair members and, of the 35 pairs concordant for any psychosis, only 4 (11.4%) were concordant for schizoaffective disorder. Of 17 siblings with schizoaffective disorder, 5 (29.4%) had a co-sibling with schizophrenia, 8 (47.1%) had a co-sibling with a mood disorder, and only 4 (23.5%) had a co-sibling with schizoaffective disorder. Moreover, those schizoaffective siblings with mood disorder co-siblings were significantly older at onset of illness than were the schizoaffective siblings with schizophrenic co-siblings. These findings are quite consistent with a fifth hypothesis, that some schizoaffective patients are genotypically schizophrenic while others comprise genotypes for mood disorder.

Similarly, Cardno et al (35) described twin-pairs of individuals with schizophrenia, schizoaffective or manic disorder. Of the 32 in which one of the pair had schizoaffective disorder, the co-twin had mania in 13 (40.6%) of the cases, schizophrenia in 10 (31.2%), and schizoaffective in 9 (28.1%). Model fitting indicated the genetic liability to the schizoaffective syndrome was "entirely shared in common with the other two syndromes." Another analysis of this cohort showed a high heritability (71%) of a lifetime history of one or more Schneiderian first-rank symptoms (36).

Finally, Laursen et al. (37) conducted a register-based cohort of 2.4 million Danes and found that the existence of a first-degree relative ever admitted with a diagnosis of ICD-8 or ICD-10 schizoaffective disorder increased an individual's risk

TABLE 7.1. Rates of illness among relatives of probands with schizoaffective, mood-incongruent, or atypical psychoses: comparisons to probands with mood disorder or schizophrenia.

	Proband Diagnosis		
	Mood disorder	Schizoaffective or equivalent	Schizophrenia
Schizoaffective probands not divided by polarity			
Reference (definition of schizoaffective disorder used in study)			
Angst, 1973 (9) (author's def.)			
No. of probands	254	73	–
MR% schizophrenia[a]	1.4	5.9	
MR% mood disorder	13.3	7.1	
MR% schizoaffective	0.7	3.8	
Tsuang et al., 1976 (10) (author's def.)			
No. of probands	325	85	200
% FH+ for schizophrenia[b]	0.5	1.3	1.3
% FH+ for mood disorder	8.3	7.6	3.1
Suslak et al., 1976 (11) (author's def.)			
No. of probands	37	10	–
MR% schizophrenia	0.9	4.0	
MR% mood disorder	12.5	6.5	
Tsuang et al., 1977 (12) (author's def.)			
No. of probands	289	52	183
MR% schizophrenia	0.5	0.9	1.3
MR% mood disorder	8.3	11.8	3.2
Mendlewicz et al., 1980 (13) (author's def.)			
No. of probands	110	55	55
MR% schizophrenia	2.5	10.8	16.9
MR% mood disorder	34.0	34.6	8.6
Scharfetter, 1981 (14) (author's def.)			
No. of probands	89	40	102
MR% schizophrenia	3.3	13.5	~7.4
MR% mood disorder	11.4	4.4	~1.0
MR% schizoaffective	3.4	2.5	–
Baron et al., 1982 (15) (RDC)			
No. of probands	85	50	50
MR% schizophrenia	0.3	2.2	7.9
MR% mood disorder	25.2	18.9	5.1
Gershon et al., 1988 (16) (RDC)			
No. of probands	161	33	24
MR% schizophrenia	0.3	3.2	3.1
MR% mood disorder	22.6	20.8	16.0
MR% schizoaffective	0.6	3.9	0.6
Kendler et al., 1995 (17) (DSM-III-R)			
No. of probands	397	159	354
MR% schizophrenia	2.2	6.4	8.0
MR% mood disorder	34.0	54.8	27.8
MR% schizoaffective	4.2	2.4	3.0
Maier et al., 1993 (18) (RDC)			
No. of probands	1,086	425	589
MR% schizophrenia	0.5	3.1	3.9
MR% mood disorder	11.2	11.8	10.7
MR% schizoaffective	0.6	3.3	2.2
Taylor et al., 1993 (19)			
No. of probands	71	76	90
MR% schizophrenia	1.9	3.5	2.7
MR% mood disorder	8.9	5.6	7.0
Schizoaffective mania vs. mania (vs. schizophrenia)			
Abrams and Taylor, 1976 (20) (RDC)			
No. of probands	78	10	–
% FH+ for schizophrenia	0	0	–
% FH+ for mood disorder	14.1	13.9	–
Pope et al., 1980 (4) (RDC)			
No. of probands	34	52	41
% FH+ for schizophrenia	0	0	9.8

(continued)

TABLE 7.1. (continued)

	Proband Diagnosis		
	Mood disorder	Schizoaffective or equivalent	Schizophrenia
% FH+for mood disorder	44.1	40.4	9.8
Rosenthal et al., 1980 (21) (RDC)			
No. of probands	28	25	–
MR% schizophrenia	0	0	–
MR% bipolar disorder	9.0	11.5	–
Andreasen, 1989 (22) (RDC)			
No. of probands	227	37	–
MR% schizophrenia	0.8	0.7	–
MR% bipolar I or II disorder	8.4	5.8	–
MR% schizoaffective bipolar	0.5	0.7	–
Bocchetta et al., 1990 (23) (RDC)			
No. of probands	65	56	–
MR% schizophrenia	0.2	0.8	–
MR% bipolar disorder	2.8	0.5	–
MR% schizoaffective, bipolar	1.4	2.9	–
Conus et al., 2010 (24) (DSM-III-R)			
No. of probands	87	21	–
% FH+for schizophrenia	10.5	30.0	–
% FH+for mood disorder	22.1	10.0	–
Schizoaffective depression vs. depression (vs. schizophrenia)			
Coryell and Tsuang 1982 (25) (DSM-III)			
No. of probands	221	95	235
MR% schizophrenia	0.5	1.6	2.8
MR% unipolar disorder	13.0	8.2	5.8
Abrams and Taylor, 1983 (26) (DSM-III)			
No. of probands	14	17	31
MR% schizophrenia	0	0	1.6
MR% mood disorder	12.9	19.3	6.8
Andreasen et al., 1987 (27) (RDC)			
No. of probands	330	18	–
MR% schizophrenia	0.3	2.5	–
MR% unipolar disorder	28.4	21.0	–
MR% schizoaffective unipolar	0.3	0	–
Coryell and Zimmerman, 1988 (28) (RDC)			
No. of probands	29	47	21
MR% schizophrenia	0	2.3	1.4
MR% unipolar disorder	25.3	22.5	11.4
MR% schizoaffective	1.0	2.5	0
Bocchetta et al., 1990 (23) (RDC)			
No. of probands	29	26	–
MR% schizophrenia	0	0.5	–
MR% unipolar disorder	3.3	3.7	–
MR% schizoaffective, unipolar	0	0.5	–
Maj et al., 1991 (29) (DSM-III-R)			
No. of probands	46	43	28
MR% schizophrenia	0.9	6.1	8.8
MR% mood disorder	15.0	3.4	1.7

[a]Morbid risk (MR) % = no. of relatives with a disorder/no. of relatives at risk for that disorder.
[b]% Family history (FH) positive = no. of probands with a family history of a disorder/total number of probands.

of being admitted for schizoaffective disorder by a factor of 1.8. A family history of schizoaffective disorder, however, also increased risks for admissions with bipolar disorder or schizophrenia by factors of 2.9 and 3.6, respectively.

Efforts to weigh the relative merits of the first four hypotheses are complicated by the growing consensus that schizophrenia and bipolar disorder probably share some predisposing alleles (38, 39). Indeed, the results of the multiple family studies, together with those of twins and sib-pairs yield no clear support for any of them. Instead, the fifth "heterogeneity" or "diagnostic uncertainty" hypothesis appears to afford the best fit. Patients with this label may, for practical purposes, be viewed in terms of the likelihood that they suffer from either schizophrenia or mood disorder. There are undoubtedly also patients with this label who are suffering from both illnesses. The prevalence figures for psychotic mood disorder and for schizophrenia indicate that such coincidences are rare and probably account for a small proportion of patients with schizoaffective disorder. This rarity, and the lack of any clear means with which to identify such a subgroup, limits the practical significance of its existence.

TABLE 7.2. Rates of illness among relatives of probands with RDC schizoaffective disorder divided by subtype.

	Proband diagnosis	
	Mainly schizophrenic	**Mainly affective or other**
Baron et al., 1982 (15)		
No. of probands	28	22
MR% for schizophrenia	4.1	0
MR% for mood disorder	10.9	28.1
Kendler et al., 1986 (40)		
No. of probands	19	28
MR% for schizophrenia	8.2	3.8
MR% for mood disorder	7.3	14.5

On the other hand, the likelihood that most schizoaffective patients have schizophrenia or mood disorder gives considerable importance to subdivisions within schizoaffective disorder. Within the mood disorders, the bipolar/unipolar distinction is well supported by family and outcome studies and is widely accepted. Its application to a group that is substantially comprised of individuals with mood disorder thus seems reasonable. Another intuitively compelling subdivision is based on the relative predominance of schizophrenic or affective features. In the RDC, schizoaffective patients who exhibit mood-incongruent psychotic features for at least 1 week without manic or depressive symptoms, or who have premorbid features suggesting schizophrenia, have the "mainly schizophrenic" subtype. The results of at least two family studies clearly support this distinction (see Table 7.2).

The DSM-IV definition of schizoaffective disorder closely resembles the RDC mainly schizophrenic subtype in that it requires a period of delusions or hallucinations without prominent mood symptoms. DSM-IV major affective disorder with mood-incongruent psychotic features, in turn, closely approximates the RDC mainly affective subtype. Not surprisingly, the only family study of DSM-IIIR schizoaffective disorder available as of this writing (29) replicates the patterns displayed in Table 7.2. The relatives of schizoaffective probands had twice the rate of schizophrenia as the relatives of probands with major depression and mood-incongruent psychotic features (morbid risk was 8.7% and 3.8%, respectively) and one-half the rate of major mood disorders (morbid risk was 2.4% and 6.5%, respectively). Notably, both Kendler et al. (40) and Maj et al. (29) provided values for normal controls.

In comparison with those controls, RDC mainly schizophrenic probands (40) and DSM-IIIR schizoaffective probands (29) had no increase in familial loading for affective disorder. Pending further replications of these patterns, we may conclude that the large majority of patients who meet these narrow definitions of schizoaffective disorder, in fact, have schizophrenia. Groups with RDC mainly affective schizoaffective disorder or with DSM-IIIR major depression and mood-incongruent psychotic features apparently retain substantial heterogeneity; familial rates of schizophrenia were substantially higher in both studies (29, 40), though not significantly so, than the rates for normal controls.

7.3. Epidemiology

Most community surveys have not described rates of schizoaffective disorder. Given the many definitions in use and the low concordance across these definitions (41), such rates would have been widely disparate. The National Institute of Mental Health (NIMH) Epidemiologic Catchment Program (42) encompassed a very broad base, but published results have used DSM-III, and as noted above, this system leaves schizoaffective disorder as a residual, non-operationalized category. Of two community surveys that used the RDC, Weissman and Myers (43) found a 0.4% lifetime prevalence for RDC schizoaffective disorder, whereas Vernon and Roberts (44) found 0.8%. These figures were based on only three and four cases, respectively, however, and the individuals were not ill when interviewed.

Brockington and Leff (41) found 10 patients who met at least three of eight definitions for schizoaffective disorder from approximately 222 consecutive admissions; 6 (2.7%) met RDC for schizoaffective disorder (1 manic and 5 depressed). These figures are similar to those derived from all consecutive admissions seen over a several year period at the University of Iowa; of 388 patients, 11 (2.8%) met RDC for schizoaffective disorder (Coryell, unpublished data). In a subsequent series of 97 consecutively admitted non-manic psychotic patients, 48.4% had RDC schizoaffective disorder, depressed type (45). In the same series, only 21 met RDC for schizophrenia. Thus, while conditions meeting one or more definitions for schizoaffective disorder may be rare in the community, they comprise a large portion of psychotic patients who come to treatment.

Some have used prevalence data to address an additional epidemiologic hypothesis—that schizoaffective disorder represents the chance coexistence of schizophrenia and affective disorder. According to Brockington and Leff (41), this chance coexistence should occur only once in a year in Great Britain, yet they found 10 in 1 year in only three hospitals.

7.4. Clinical Picture

A description of the clinical picture seen in schizoaffective disorder is necessarily circular. Most definitions of schizoaffective disorder depend entirely on the clinical picture, and since these definitions vary so markedly (41), the associated clinical picture also will vary depending on the label. By definition, then, patients with RDC schizoaffective disorder, and those with DSM-III or DSM-IIIR mood disorder and mood-incongruent psychotic features, can exhibit in cross section any symptom characteristic of mood disorder. Such a patient may report low mood, anorexia, insomnia, fatigue, and thoughts of suicide, as well as thought broadcasting, delusions of passivity, and hallucinations in any sphere. He or she may also exhibit euphoria, hyperactivity, recklessness, and grandiosity, as well as a blunted affect, bizarre behavior, catatonia, and loose associations. By definition, schizoaffective disorder differs from mood disorder because of the presence of schizophrenic features. In turn, the presence of affective symptoms distinguishes schizoaffective disorder from schizophrenia.

Phenomenological differences may extend further, however. In one study, patients with RDC schizophrenia had delusions that were significantly more bizarre than those reported by schizoaffective patients. Schizophrenic patients also were more likely to exhibit loosening of associations and a blunted or inappropriate affect (45). Moreover, when compared with patients with psychotic major depression, schizoaffective patients reported a lesser severity of 12 depressive symptoms, and these were largely confined to endogenous rather than nonendogenous depressive symptoms. This difference in endogenous symptom severity emerged in another sample as well (46). Thus, broadly defined, *schizoaffective depression* designates patients who have depressive syndromes that are less typical than those of patients with psychotic depression and schizophrenic symptoms that are less typical than those of schizophrenic patients. These patterns support a "heterogeneity" hypothesis.

Because these patients suffer from a psychosis, an associated loss of insight, and often, a psychomotor disturbance, many are poor historians. This deserves special emphasis because, at the time of admission, affective symptoms may be altogether overshadowed by the patient's delusional preoccupation, hallucinations, or bizarre behavior. Indeed, at this point such patients often deny mood symptoms that they later recall and that other informants describe when questioned carefully. The distinction between affective, schizoaffective, and schizophrenic psychosis, therefore, must not depend on the patient interview alone. In all cases the clinician must seek knowledgeable informants to learn whether affective symptoms preceded the psychotic ones. Serial interviews of the patient are also more useful than is generally appreciated (47).

7.5. Clinical Course

The prognosis for schizoaffective disorder appears to be worse than that for mood disorder (see Table 7.3), although a small number of studies have yielded results to the contrary. Proportions with good outcomes vary widely across studies, and this reflects such methodological particulars as the length of follow-up and the definitions of good outcome. The prognostic differences between schizoaffective and mood disorders also vary and appear to reflect important differences in how schizoaffective disorder is defined. Specifically, schizoaffective patients so identified because of the persistence of schizophrenia-like symptoms between affective episodes, as in DSM-IV, may constitute a different group from those defined solely by the presence of first-rank symptoms in the midst of an affective syndrome. The studies finding the largest outcome differences between mood disorder and schizoaffective disorder were those which defined the latter disorder by the persistence of schizophrenia-like symptoms between affective episodes (48–52). In contrast, one of the few studies finding a superior outcome for schizoaffective disorder explicitly excluded subjects with "long periods of psychosis in the absence of an affective syndrome" (21).

As the occurrence of psychotic features outside of affective episodes portends the eventual chronicity of psychotic features, so does the presence of psychotic features within the affective syndrome appear to predict the persistence of affective symptoms. This seems to be equally so whether psychotic features accompany manic or depressive syndromes (8). Among affectively ill individuals with psychotic features the quality of those features has added prognostic importance. A review of thirteen studies that compared mood-congruent and mood-incongruent psychotic features consistently showed at least a somewhat poorer outcome for patients with mood-incongruent features (72).

The heterogeneity that remains among patients with affective illness plus mood-incongruent psychotic features has rarely been explored but may have prognostic relevance. Conus et al (73) showed this when they described 12-month outcomes among patients with psychotic mania. After adjustment for age, sex, age-of-onset, and duration of psychotic symptoms, the presence of first-rank symptoms was predictive of a poorer quality of life scores and greater negative symptoms while the presence of mood-incongruent psychotic features per se failed to predict any of the five outcome measures.

Because lithium is generally thought to be effective in mania and much less so in schizophrenia, acute and prophylactic response to this drug affords another view of the variability within schizoaffective disorder. With one exception, lithium studies that have described five or more patients with schizoaffective mania have reported poorer responses in that group than in more typically manic groups (see Table 7.4). Subdivisions within schizoaffective groups are probably very meaningful to response

TABLE 7.3. Course of illness among patients with schizoaffective, mood-incongruent, or atypical psychoses: comparisons to probands with affective disorder or schizophrenia.

	Mood disorder	Schizoaffective or equivalent	Schizophrenia
Schizoaffective disorder not divided by polarity			
Reference (definition of schizoaffective disorder used in study)			
Tsuang et al., 1976 (10) (author's def.)			
No. of patients	325	85	200
% "recovered"	58	44	8
Angst, 1980 (53) (author's def.)			
No. of patients	254	150	–
% with "full remission"	39	27	–
Himmelhoch et al., 1981 (49) (author's def.)			
No. of patients	409	34	–
% "improved" within 2 months"	39.7	5.9	–
Moller et al., 1988 (54) (ICD)			
No. of patients	36	27	34
% with "favorable outcome"	84	78	65
Grossman et al., 1991 (55) (RDC)			
No. of patients	40	41	20
% with outcomes better than "very poor"	84	57	45
Williams and McGlashan, 1987 (56) (author def.)			
No. of patients	63	68	163
% recovered/good outcome	43	22	14
Moller et al., 1988 (54) (RDC)			
No. of patients	36	27	34
% with outcome GAS >50	65	78	84
Moller et al., 2000 (57) (ICD-9)			
No. of patients	48	68	85
Mean maximum GAS			
Score in final year	7.5	69	60
Sim et al., 2007 (58) (DSM-IV)			
No. of patients	–	24	254
Mean (SD) PANSS	–	42.0 (12.7)	35.0 (8.4)
Schizoaffective mania vs. mania (vs. schizophrenia)			
Brockington et al., 1980 (59) (author's def.)			
No. of patients	66	30	53
% recovered	94	77	34
Abrams and Taylor, 1976 (20) (presence of FRSs)			
No. of patients	78	10	–
Mean treatment response (4 = full remission)	3.2	3.5	–
Pope et al., 1980 (4) (RDC)			
No. of patients	18	35	27
% with "marked improvement" after treatment	79	73	7
% with "excellent" globally assessed outcome	44	26	0
Rosenthal et al., 1980 (21) (RDC)			
No. of patients	28	25	–
Probability of remaining well at 16 weeks	70	86	–
van Praag and Nijo, 1984 (60) (RDC)			
No. of patients	21	10	19
% with "good" treatment responses after 6 weeks	62	40	5
Grossman et al., 1984 (61) (RDC)			
No. of patients	33	15	47
% with "good" overall functioning	33	13	9
Maj et al., 1985 (62) (RDC)			
No. of patients	16	17	–
Mean score (SD) on Strauss–Carpenter Outcome Scale (16 = optimal score)	13.7 (2.6)	12.6 (1.7)	–
Coryell et al., 1990 (7) (RDC)			
No. of patients	56	14	–
% recovered from index episode	95	79	–
Marneros et al., 1990 (63) (author's def.)			
No. of patients	30	56	–
% with "no difficulties"	66.7	46.4	–

(continued)

TABLE 7.3 (continued)

	Mood disorder	Schizoaffective or equivalent	Schizophrenia
Tohen et al., 1992 (64) (DSM-III)			
No. of patients	24	30	–
Median time in remission	33	8	–
Conus et al., 2010 (24) (DSM-III-R)			
No. of patients	61	18	–
Mean (SD) QLS function level (total score)	93.3 (23.6)	72.9 (25.0)	–
Marneros et al., 2009 (65) (DSM IV)			
No. of patients	62	120	–
% with good social adaptation	36.1	35.6	–
Moller et al., 2011 (66) (DSM IV)			
No. of patients	114	22	–
% with episodic remitting course	92	88	–
Schöttle et al., 2012 (67) (DSM IV)			
No. of patients	98	36	–
% with remission of positive symptoms	80.6	61.1	–
Schizoaffective depression vs. depression (vs. schizophrenia)			
Brockington et al., 1980 (68) (author's def.)			
No. of patients	66	75	53
% recovered	94	69	34
Coryell and Tsuang, 1982 (25) (presence of MIPFs)			
No. of patients	149	43	171
% recovered during follow-up	57.1	32.6	7.0
Abrams and Taylor, 1983 (26) (DSM-III)			
No. of patients	14	17	31
Mean % improvement	80.7	92.7	34.5
van Praag and Nijo, 1984 (60) (RDC)			
No. of patients	29	12	19
% with "good" treatment response after 6 weeks	69	50	5
Grossman et al., 1984 (61) (RDC)			
No. of patients	330	24	–
% with "good" overall functioning	38	8	9
Maj et al., 1985 (62) (RDC)			
No. of patients	23	19	
Mean score (SD) on Strauss–Carpenter Outcome Scale (16 = optimal score)	13.3 (2.5)	11.6 (3.6)	
Coryell and Zimmerman, 1986 (69) (RDC)			
No. of patients	29	46	20
% recovered during follow-up	59	39	10
Opjordsmoen, 1989 (70) (DSM-III)			
No. of patients	50	33	94
% "healthy" at follow-up	66	42	10
Coryell et al., 1990 (6) (RDC)			
No. of patients	73	30	
% recovered from index episode	89	73	
Marneros et al., 1990 (71) (author's def.)			
No. of patients	76	45	
% with "no difficulties at follow-up"	63	56	
Tsuang and Coryell, 1993 (51) (DSM-III-R)			
No. of patients	32	11	22
% recovered	44	0	0
Coryell and Tsuang, 1985 (46) (presence of MIPFs)			
No. of patients	101	89	219
% with good outcomes (mental)	62	45	21

prediction, but few studies have considered them. Maj (74) did find that the RDC subtyping strongly predicted prophylactic response to lithium. Those with the mainly affective subtype, but not those with the mainly schizophrenic subtype, showed a significant reduction in number of episodes with lithium therapy.

Such comparisons serve to summarize the literature but their simplicity can be misleading since there are many shades of "response," "improved," and "recovered." In light of the most tenable hypothesis on etiology, some schizoaffective patients should have a course typical of psychotic affective disorder; the psychosis may be profound, but eventual recovery is complete.

TABLE 7.4. Outcome with lithium therapy in patients with schizoaffective (or equivalent) mania: comparisons to patients with manic disorder.

	Manic disorder	Schizoaffective mania
Reference (definition of schizoaffective disorder used in study)		
Schou et al., 1954 (75) (author's def.)		
No. of patients	30	8
% with "+ effect" acutely or prophylactically	40	25
Baastrup and Schou, 1967 (76) (author's def.)		
No. of patients	51	15
% reduction of no. of episodes with lithium	95	71
Zall et al., 1968 (52) (author's def)		
No. of patients	33	10
% with "complete recovery"	79	10
Angst et al., 1970 (48) (WHO criteria)		
No. of patients	114	72
% with improvement in frequency of episodes with lithium	67	49
Aronoff and Epstein, 1970 (77) (author's def.)		
No. of patients	7	6
% with "unequivocal" acute response	71	33
Johnson, 1970 (50) (author's def.)		
No. of patients	19	11
% in "remission"	79	9
Prien et al., 1974 (78) (author's def.)		
No. of patients	86	5
% without episodes during 1 year of prophylaxis	60	40
Pope et al., 1980 (4) (RDC)		
No. of patients	13	20
% with "marked" improvement	92	80
Rosenthal et al., 1980 (21) (RDC)		
No. of patients	27	15
Probability of remaining well after 16 weeks	0.70	0.86
Yazici et al., 1999 (79) (presence of MIPFs)		
No. of patients	92	49
% good response	73	37
Maj et al., 1985 (62) (presence of MIPFs)		
No. of patients	63	16
% good response	52	19

Others may display a waxing and waning of symptoms, which might be perceived initially as recovery and relapse but which eventually evolves into the chronicity and avolition characteristic of narrowly defined schizophrenia. Patients, as well as families and physicians, need to know which course is more likely for a given individual.

Findings from the National Institute of Mental Health Collaborative Program on the Psychobiology of Depression bear directly on this issue (6, 7). These analyses sought to predict the presence or absence of a persistent psychosis 5 years in the future for patients who presented with psychotic affective or schizoaffective disorders. Overall, such outcomes emerged in 24 individuals, or 14 percent of the sample. For patients who were depressed at intake, only a history of mood-incongruent psychotic features to the relative exclusion of depressive symptoms significantly and independently predicted persistent psychosis (6). Among those who were manic at intake, significant and independent predictors consisted of a history of any formal thought disorder in the absence of prominent manic symptoms, loosening of associations, and greater global severity at intake. When manic and depressed patients were pooled (7), a stepwise regression analysis revealed the following independent predictors of a sustained psychotic outcome, in order of robustness: longer duration of index episode, history of psychotic features that had occurred at some point in the absence of (or to the exclusion of) affective symptoms, poor adolescent friendship patterns, having never been married, and the absence of a history of mania. Few other reports have attempted to predict schizophrenia-like outcomes in such a sample, but the most important of these yielded very similar results. Brockington et al. (68) selected as the single most valuable predictor of such an outcome "the presence of schizophrenic symptoms in the absence of affective symptoms."

Early work with the dexamethasone suppression test (DST) suggested a high level of specificity for psychotic depression and it appeared to hold promise as a clinically useful diagnostic tool. Subsequent research showed that nonsuppression rates among schizophrenics, while consistently lower than those for patients with psychotic depression, are nevertheless higher than those for normal controls (80). It now appears that nonsuppression among individuals with narrowly defined schizophrenia has a different meaning from nonsuppression among patients with psychotic depression or mania. In particular, nonsuppression among

schizophrenic patients appears to be associated with relatively prominent negative features (81–84). Nonsuppression may nevertheless have prognostic significance among other patients with depression and psychotic features, i.e., those with psychotic major depression or schizoaffective depression. Two studies (85, 86) have found that among such patients, nonsuppressors are substantially more likely to be free of psychotic features at the end of follow-up (1 and 8 years, respectively). Another reported that nonsupression occurred in four of five individuals with baseline diagnosis of schizophrenia but with a follow-up diagnosis of schizoaffective disorder. Nonsuppression occurred in only two of the seven of those whose diagnosis shifted from psychotic major depression to schizoaffective disorder (87). The DST was not predictive in another follow-up study of schizoaffective disorder (88) but this sample included only four nonsuppressors and the analysis did not use persistent psychosis as an outcome measure.

7.6. Differential Diagnosis

As with other conditions seen by psychiatrists, the differential diagnosis when affective and psychotic symptoms coexist should begin with the distinction between conditions that arise from demonstrable lesions (due to medical conditions) and those that do not. Depressive, manic, and schizophrenic syndromes can be produced by a variety of identifiable insults, and the differential diagnosis for each of these conditions is provided in more detail in the corresponding chapters. With those other possibilities in mind, there are several general features that should increase the suspicion that psychiatric symptoms are arising from a medical condition. "Depression" with only two or three of the possible eight criteria symptoms should raise such suspicions, as should the appearance of affective or psychotic symptoms in an elderly individual with no prior psychiatric history. Confusion that is out of proportion to the depressive symptoms and that features approximate answers rather than refusal or reluctance to answer also increases the possibility of medical illness as etiology. Likewise, "catatonia" in an individual with no recent or remote history of affective disorder or schizophrenia should be considered undiagnosed until a full syndrome can be identified.

Several conditions are of particular note in the differential diagnosis of schizoaffective syndromes. High doses of exogenous steroids may produce conditions in which symptoms of mood disorder, schizophrenia, and delirium alternate rapidly. Liability to this condition is dose-related, and symptoms typically resolve within 3 weeks, rarely lasting longer than 6 weeks (89). The crucial feature here is the history of high doses of steroids preceding the onset of the symptoms. Because this history is almost always apparent, diagnosis is usually not a problem. Patients with persistent symptoms, particularly those with a prior history of similar symptoms not preceded by steroid ingestion, may, however, have a purely functional condition (89).

Amphetamines and other sympathomimetics may produce hyperactivity, euphoria, racing thoughts, and pressured speech typical of mania shortly after ingestion. A "crash" may occur after several days of continuous amphetamine ingestion and often features dysphoria, hyperphagia, hypersomnia, and irritability—a picture that may resemble depression. These conditions rarely, of themselves, lead individuals to seek psychiatric help. Between these two phases of amphetamine intoxication, however, a psychosis may emerge that is indistinguishable from paranoid schizophrenia in cross section. Delusions typically resolve within several days to 1 or 2 weeks, and simple observation over this period usually clarifies the diagnosis.

Phencyclidine (PCP) intoxication may be more difficult to recognize. The diagnosis is frequently missed, even by those who are familiar with its presentation (90). This may be due in part to the protean nature of the symptoms; paranoid delusions with a clear sensorium may alternate with marked depressive symptoms, or these syndromes may coexist with or without evidence of delirium. However, this condition often involves certain physical symptoms that may help to distinguish it from functional psychosis—slurred speech, ataxia and nystagmus, ptosis, hypertension, analgesia, and hyperreflexia. The level of suspicion also should depend in large part on the patient's demographic features and the pattern of drug use in the patient's subculture.

Temporal lobe epilepsy also may produce affective psychosis, schizophrenia-like psychosis, or a mixture of the two (91), and the syndromes can closely resemble their functional counterparts (92). In only 3 of the 69 cases described by Slater and Beard (92) did the psychosis and epilepsy begin in the same year; in all other cases the psychosis followed the epilepsy, usually by many years. Thus the likelihood that epilepsy lies at the base of a new case of psychosis is greatly reduced when there is no history of clinically manifest seizures.

7.7. Treatment

Clinicians should consider the hypotheses described previously when selecting treatment. The most efficient approach, the one most consistent with follow-up and family history data, assumes that a schizoaffective patient has either schizophrenia or mood disorder. The clinician must weigh the probability of one of these illnesses over the other using all available data—demographics, present and past psychopathology, premorbid or prodromal features, and family history.

Emphasis should be given to the mood disorder alternative, particularly in treatment-naïve patients, since treatment of mood disorders is generally more specific than treatment of schizophrenia. For instance, ECT is much more effective for psychotic depression than for schizophrenia, and the prophylactic value of lithium in mood disorder is clearly established, while there is relatively little support for its use in schizophrenia. In contrast, antipsychotics ameliorate psychotic symptoms regardless of the underlying disorder. Because of the long-term risk of tardive dyskinesia with typical antipsychotic treatment, and of dyslipidemias and weight gain with atypical antipsychotics, other more specific approaches—lithium, antidepressants, and ECT—should be given preference unless indications for chronic antipsychotic treatment are clear.

A recent meta-analysis has shown that a combination of antidepressant and antipsychotic is more effective in the treatment of psychotic depression than is monotherapy with either drug class (93). Numbers needed to treat (NNT) were 7 for the combination treatment compared to antidepressant monotherapy and 5 for a combination therapy compared to antipsychotic monotherapy. The question of how long combination treatment should be maintained is an important but currently open question.

In the absence of clear indications for long-term use of antipsychotics, these drugs should be discontinued gradually when delusions remit. The clinicians should then determine whether a mood stabilizer or an antidepressant is likely to provide adequate protection against relapse. This requires careful surveillance, particularly in the first 6 months, when the risk of relapse is the highest (94). Because relapse is likely to involve a loss of insight, the family's help will be important in this effort. After one or more episodes, they are likely to learn the early warning signs and be able to help the patient to seek early intervention.

More judgments are necessary when relapse does occur. Was the relapse preceded by poor compliance? If so, does the patient find the side effects peculiar to that drug intolerable, or does he or she simply require more time to develop the acceptance and habits necessary for adequate compliance? In the case of bipolar disorders the options for effective prophylaxis are limited and it is important not to abandon a given drug prematurely. Also, it must be remembered that prophylactic efficacy may require time to develop. In fact, maintenance therapy may take several years to show clear protective effects for depression or mania (95).

7.8. Schizophreniform Disorder

Langfeldt coined the word schizophreniform in 1939 (96) to describe schizophrenia-like psychoses with relatively good prognoses. He intended this to be a heterogeneous group that would include "exogenically precipitated psychosis" (97). Indeed, the words schizophreniform and schizoaffective have been used interchangeably through much of the subsequent literature. In DSM-5, however, individuals who meet criteria for schizoaffective disorder are excluded from these diagnoses. Either no major mood episodes have occurred during the period of illness, or if they have, the major mood syndrome has been present for a minority of the total duration of the illness. Criterion A for schizophreniform disorder is identical to Criterion A for schizophrenia but the duration for schizophreniform disorder is less than 6 months. DSM thus sets schizophreniform disorder apart both from mood disorder with mood-incongruent psychotic features and from schizoaffective disorder. This departure from convention must be borne in mind in any review of recent literature on atypical schizophrenia. The preceding section under schizoaffective disorder describes schizophreniform disorder equally well, according to the definitions in use before DSM-III. This section is, therefore, restricted to studies using the DSM definitions.

Table 7.5 summarizes the studies that described at least 10 patients with schizophreniform disorder and that included comparisons with other diagnostic groups. Nine of ten studies suggest that, like schizoaffective disorder, schizophreniform disorder defines an intermediate or heterogeneous group (45, 98–101).

In some cases, though, the comparison measures placed schizophreniform disorder closer to schizophrenia though in others, schizophreniform disorder had a closer resemblance to the mood disorders.

Consensus may not be forthcoming for several reasons. First, the proportion of mood disorder comparison groups with psychotic features probably differs across studies and psychotic features themselves have adverse effects on outcomes (6–8). Second, the distinction between schizophrenia and schizophreniform disorder often hinges on the presence of a prodromal syndrome and many of the components of this syndrome (i.e., social isolation, blunted affect, and digressive speech) shade gradually into the normal spectrum of behavior. Acutely psychotic patients are often unable to give valid accounts of such features in retrospect. Affective syndromes may also be difficult to assess in patients who are delusional or hallucinating. Even when such patients report typical depressive symptoms, these are often attributed to understandable effects of acute psychosis. A careful history taken from knowledgeable informants will remedy these problems to some extent. Unfortunately, few studies describe the availability of such informants or the thoroughness with which they were interviewed. Reasons for discordance across these studies are, therefore, hard to trace.

In light of this, the clinician must maintain doubtfulness about the true nature of schizophreniform disorder in a given case. As with schizoaffective disorder, the clinician should use all the clinical data available to weigh the likelihood of schizophrenia over an affective disorder, giving at least initial weight to the presumption that the overall course and treatment response will ultimately suggest a mood disorder.

TABLE 7.5. DSM-IIIR schizophreniform disorder: studies of validity[a].

Study	No. with SF	Comparison groups	Design	Results
Coryell and Tsuang, 1982 (25)	93 (of 810 admissions studied: 11.5%)	86 bipolar MD 203 unipolar MD 214 S	Chart follow-up averaging 3.1 years; family history study	16% of SF patients recovered vs. 8% of S patients and 58% of MD patients; SF resembled S patients more than MD patients in terms of MR for S and MD
Weinberger et al., 1982 (102)	35 (of 128 with CT scans: 27.3%)	17 S 23 mood disorder 27 other disorders 26 neurologic controls	Computed tomographic study (CTs routinely obtained)	SF group had distribution of ventricular to brain ratio indistinguishable from those for S group, significantly less than controls, less (but not significantly) than other psychiatric illnesses
Targum, 1983 (101)	21 (of 145 admissions: 14.5%)	86 MD 24 other disorders 14 S	Neuroendocrine evaluation (DST and TRH-ST) with 6-month follow-up of only SF patients	% with: +DST, Blunted TRH-ST MD 44 32 SF 24 29 S 7 7 Neuroendocrine test results predicted outcome among SF patients
Coryell and Zimmerman, 1986 (69)	93	298 MD 219 S	Systematic follow-up of 40 years	SF patients were significantly more likely than MD patients, but only slightly less likely than S patients, to be symptomatic at follow-up
Makanjuola and Adedapo, 1987 (103)	34	66 S	25–38 months follow-up	16% of SF and 43 % of S actively psychotic or residual symptoms of schizophrenia on follow-up
Beiser et al., 1988 (98)	29 (of 575 patients with nonorganic psychosis: 4.5%)	60 S 73 MD	Systematic follow-up of 18 months	18 (62.1%) re-diagnosed as schizophrenic on follow-up; 8 others (27.6% of the sample) had recovered
Kendler and Walsh, 1995 (104)	18	126 S	Follow-up and family study	SF had better functioning on follow-up than S, similar to MD; SF had less S in relatives than those of S probands but more than controls
Fennig et al., 1994 (105)	11	57 S	Diagnostic stability over months follow-up	7 (63.6%) retained SF diagnosis; 3 (27.3%) re-diagnosed as S
Schimmelman et al., 2005 (106)	190	113 S 34 schizoaffective 13 MD	Diagnostic stability over 18 month follow-up	Only 76 (40.0%) retained SF diagnosis; 100 (52.6%) re-diagnosed as S
Whitty et al., 2005 (107)	15	31 psychotic MD	4-Year follow-up	67% of SF and 16% of MD groups had final diagnosis of S
Naz et al., 2003 (108)	34	128 S	2-Year follow-up	SF significantly more likely to have remission at 6+24 months than S

[a]*MD* mood disorder, *SF* schizophreniform disorder, *S* schizophrenia, *DST* dexamethasone suppression test, *TRH-ST* thyroid-releasing hormone stimulation test.

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8
Delusional Disorders

Marc-André Roy, M.D., FRCPC*

Abstract Delusional disorders are characterized by delusions in the absence of any other psychiatric illness that could account for the delusional thought processes. DSM-5 lists erotomanic, grandiose, jealous, persecutory, somatic, mixed, and unspecified subtypes. The prevalence of delusional disorders has been estimated to be 0.18 %. The available evidence does not suggest a shared predisposition with either schizophrenia or mood disorders, but very little is known about its neurobiology. The course of the illness is highly variable; some cases recover rapidly and completely but in others it runs a chronic course. Conditions to be excluded before diagnosing a delusional disorder include paranoid schizophrenia, psychotic mood disorder, dementia, drug-induced psychotic disorder, paranoid personality disorder, and hypochondriasis. Pimozide has been the preferred antipsychotic agent for delusional disorders, particularly the somatic subtype, but in recent years there has been a steady trend toward treating delusional disorders with second generation antipsychotic agents. Some therapists are now using cognitive-behavioral therapy in these patients as well.

Keywords Delusion · Persecutory delusional disorder · Jealous delusional disorder · Grandiose delusional disorder · Delusional parasitosis

8.1. Definition

Delusions are among the most common psychotic symptoms. Forty-eight percent of manic patients and 33 percent of bipolar depressives are delusional (1), and practically all patients with schizophrenia experience delusions at some time during the course of their illness. Therefore, if the concept of a delusional disorder is to have any validity as a diagnostically pure group, it must be defined by delusions in the absence of other psychiatric illness that might account for the delusional thought process. Delusions are false beliefs based on an idiosyncratic interpretation of reality; they are rigidly adhered to so that contradictory evidence is reinterpreted in a manner consistent with the belief rather than the belief being modified by the evidence.

The term *paranoia* dates back to Hippocrates, but Kahlbaum in 1863 was the first to use it to designate a diagnostically separate group of disorders that remained so over their course (2, 3). Kraepelin in 1921 further developed the concept of paranoia as a chronic and unremitting system of delusions that was distinguished from schizophrenia by the absence of hallucinations and other psychotic features. These ideas were incorporated into the first diagnostic manual (DSM-I) of the American Psychiatric Association (4). Paranoid reactions were defined as illnesses with persistent persecutory or grandiose delusions, ordinarily without hallucinations, and with emotional responses and behavior consistent with the ideas held. Subtypes included paranoia, a chronic disorder characterized by an intricate and complex delusional system, and paranoid state, usually of shorter duration and lacking the systematization of paranoia. These concepts of paranoid disorders and their subtypes have been preserved in all their essential features by DSM-II (5) and in DSM-III (6) as Paranoia and Acute Paranoid Disorder.

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M.-A. Roy, M.D., FRCPC (✉)
Professeur Agrégé, Département de Psychiatrie et Neurosciences, Université Laval, Centre de Recherche de l'Institut Universitaire en Santé Mentale de Québec City, Québec, QC, Canada
e-mail: marc-andre.roy@crulrg.ulaval.ca

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Beginning with DSM-III-R, continuing in DSM-IV and then DSM-5, the paranoid disorders were renamed *delusional disorders*, because of the confusion arising from the use of the term paranoia in its narrow meaning, e.g., persecutory delusion (7–9). The delusional disorders have been expanded to include persecutory, erotomanic, grandiose, jealous, somatic mixed, and unspecified types. As will be explained below, with the advent of DSM-5, the somatic subtype has a more restrictive definition, due to which pre-DSM-5 literature on this entity may not generalize to the now more restricted category.

International Classification of Diseases (ICD)-10 has also adopted the term *delusional disorders* to replace the *paranoid states* used in ICD-9 and classifies it under *Persistent Delusional Disorders* (10). No subtypes of delusional disorder are specified, but *Other Persistent Delusional Disorders* includes delusional dysmorphophobia, involutional paranoid state, and paranoia querulans.

Both DSM-5 and ICD-10 require delusions in the absence of schizophrenia, mood disorder or a toxic, metabolic or neurological disorder. DSM-5 requires a minimum duration of 1 month, and ICD-10 specifies that the delusions be present for a "few months." DSM-5 further specifies that functioning is not markedly impaired and behavior not odd or bizarre, apart from the impact of the delusion. Occasional auditory hallucinations do not exclude the diagnosis by either set of criteria, as long as they are not prominent. Folie á Deux, was no longer classified as a delusional disorder but as a separate psychotic disorder: *shared psychotic disorder* in DSM-IV, and was dropped from DSM-5, while remaining as *induced psychotic disorder* in ICD-10.

8.2. Epidemiology

Delusional disorders are encountered infrequently in general psychiatric practice, but this may be an under-representation of their true prevalence because these individuals tend to avoid psychiatric assessment due to their lack of insight and may escape clinical attention in the context of absence of grossly disturbed behavior. There are clear indications that delusions of parasitosis are not rare in dermatology clinics (11). Moreover, several surveys have shown that delusion-like beliefs may be frequently found in the general population (12). Thus, it is difficult to have a clear picture of the epidemiology of these disorders, and any numbers reported are likely to be underestimated.

Numbers traditionally provided in the literature illustrate this probable underestimation. Indeed, the prevalence has been traditionally estimated to be 24–30 cases per 100,000 population (i.e., 0.024–0.030%) and their annual incidence to be at 0.7–3.0 new cases per 100,000 population (13). These numbers contrast with newer data from Finland (14), using a very comprehensive sampling strategy and ascertaining psychiatric diagnoses from several sources of information, which support that delusional disorders may be considerably more frequent, with lifetime prevalence estimated at 0.18%. Despite the fact that the numbers are 6–7.5 times higher than the traditional estimates reported above, the authors considered that these higher numbers may still underestimate the true prevalence of delusional disorder given the difficulty to identify such cases in a single interview due to the often plausible character of the delusional beliefs encountered in delusional disorders.

Delusional disorders are most likely to appear in mid-life. Age at onset and age at first admission both peak in the fourth to fifth decade and range from adolescence to senescence. The sexes are affected approximately equally, although studies have found a slight excess of females, 55 percent of first admissions being women (13).

8.3. Etiology and Pathophysiology

Delusional disorders have been a relatively neglected area of psychiatric research, and consequently, the literature on etiology is quite limited, typically consisting of case series. Because schizophrenia and depression can both present with delusions, the question arises whether delusional disorders represent a separate group of disorders or simply atypical forms of these more common conditions. This question is important because of the obvious treatment implications.

If delusional disorders were a form of either schizophrenia or mood disorders, the incidence of these latter conditions should be increased in the families of delusional disorder patients, but this has not been found. Indeed, available studies have found, in relatives of delusional disorder probands, rates of schizophrenia and mood disorders that did not differ from those reported in the general population. Kendler and Walsh (15) found that the rates of schizophrenia, schizophrenia spectrum disorders, and affective illness in the relatives of eight patients with delusional disorder did not differ from the rates found among relatives of controls. Since only 59 relatives of delusional disorder probands were assessed by interview or hospital records, the power of the sample to detect differences was limited.

Reanalysis of data from a large adoption study of schizophrenia did not find a higher rate of delusional disorders in the biologic relatives of schizophrenic adoptees than in other groups of relatives (adoptive relatives of the same adoptees and biologic and adoptive relatives of control adoptees) (16). The observations indicate that Kahlbaum's original concept of paranoid disorders as uncommon but distinct entities may be correct since they appear genetically distinct from the other psychoses.

TABLE 8.1. Family history of delusional disorder.

	Simple delusional	Hallucinatory delusional	Paranoid schizophrenia
Number of cases	101	38	118
Number of relatives	643	285	653
Affective disorder (%)	1.6	1.8	2.1
Schizophrenia (%)	0.5	1.8	1.5
Paranoid traits (%)	2.3	1.1	0.6

Crowe, RR: unpublished data.

However, it should be stressed that these genetic epidemiological studies of delusional disorders typically relied on small samples and/or on diagnoses in relatives based on the family history method (i.e., diagnoses based on information from relatives) rather than on direct interviews with the relatives. Such limitations warrant cautiousness before definitely concluding that delusional disorders are genetically unrelated to schizophrenia.

While there is no evidence suggesting that delusional disorders overlap genetically with either mood or schizophrenic disorders, there is some evidence suggesting an excess of paranoid disorders or traits in relatives of delusional disorder patients. These findings suggest that these two conditions may be genetically related. Our own unpublished data (see Table 8.1) confirm these findings. We reviewed the medical records of 257 patients with either simple delusional disorders, hallucinatory delusional disorders, or paranoid schizophrenia. We reviewed all available information on relatives and assigned them blind diagnoses. As can be shown, the relatives of patients with simple delusional disorders were characterized by a higher prevalence of paranoid traits and a lower frequency of schizophrenia compared with the relatives of schizophrenic subjects, while the relatives of hallucinatory patients were between these two groups. However, only the rates of paranoid traits reached statistical significance. It should also be emphasized that such paranoid traits have also been found to co-aggregate with schizophrenia.

Very little information on the neurobiology of delusional disorders is available. A structural magnetic resonance imaging study found larger ventricles in late onset delusional disorders compared to late onset schizophrenia, both groups having larger ventricles than normal controls (17). A study of eye tracking performance reported deficits in delusional disorders similar to those reported from other research on schizophrenia (18). Together, these studies do not suggest qualitative differences concerning the neurobiology of delusional disorders compared to that of schizophrenia, although there are insufficient data to draw any firm conclusions. More recently, studies on the cognitive processes leading to delusions have received some attention, although more so in the context of schizophrenia than in the context of delusional disorders. These studies have proposed that some cognitive biases (e.g., jumping too rapidly to conclusions or a higher sensitivity to threat) may be the mechanism through which delusions occur (19).

8.4. Clinical Picture

The hallmark of the delusional disorders is the delusional system. This consists of a unique set of false ideas that are rigidly adhered to despite all contradictory evidence. The uniqueness of the delusion distinguishes these patients from persons with idiosyncratic ideas shared by a larger social group, such as a religious cult. The fixed quality of the delusion also separates them from nondelusional persons with unusual ideas. A third feature of delusions is that facts are reinterpreted to fit the delusion, rather than the delusion being modified to fit the facts. The delusion is thus characteristically fed by constant misinterpretations of the facts. It is important to emphasize that the chronic delusional patient does not base the delusional beliefs on hallucinations. For example, the paranoid patient on seeing persons laughing will think they are laughing at him or her. The perception of persons laughing is correct; it is the interpretation of the perception that is abnormal.

The delusions of delusional disorders are usually systematized and encapsulated to varying degrees. *Systematization* refers to the ramifications of the delusional system being connected by a common theme. *Encapsulation* refers to thought processes outside the delusional system remaining unaffected. As the French psychiatric tradition has emphasized, delusions can vary quite a lot in their degree of *extension*. This term refers to the extent of ramification. For example, an *unextended* delusion would be limited to a relatively small sphere of the person's life, while an *extended* delusional system might infiltrate most of the person's activities. However, even in these extreme cases, thought processes outside the delusional system remain unaffected.

DSM-IV stipulated that in delusional disorders the quality of the delusions was not bizarre and considered delusions bizarre if they were "clearly implausible, not understandable, and not derived from ordinary life experiences" (8). However, the reliability of the distinction between bizarre and non-bizarre delusions has been shown to be very poor (20) because of which this criterion was dropped in DSM-5, although DSM-5 includes a specifier to be rated when delusions are deemed bizarre (9).

Many delusional disorders are accompanied by hallucinations which, however, should not be sufficiently prominent to justify a diagnosis of schizophrenia; somatic hallucinations are recognized to be important features in several cases of delusional infestation.

When a thought disorder is present, it is not prominent and does not affect communication as does the thought disorder often observed in schizophrenia. Winokur (21) found loquacity and circumstantiality in 30% of his cases. When this occurs, it usually accompanies descriptions of the delusional system.

Another hallmark of the delusional disorders is the relative preservation of personality. Outside the areas of life involved in the delusional system, patients do not show major impairments in areas such as housework, occupational performance, and social relationships. However, the impairments of delusional patients can be severe, particularly if their delusions are extended to involve many areas of their life. Their behavior will seem normal when their delusions are not discussed or acted on, and they will show neither blunted nor discordant affect. When present, these impairments should be easily explained by the delusions. For example, a person could have problems at work because of a conviction of being persecuted; other than that, the individual's performance should remain relatively unimpaired. This impairment is often further aggravated by the characteristic tendency of these patients to act on their delusions. For example, the person who feels persecuted may complain to the police or attempt revenge; the erotomanic, convinced he is loved, may write or otherwise attempt to contact or stalk the object of his delusion. This is an area that the clinician should always inquire about given the potential consequences of these acts.

DSM-5 outlines seven subtypes that closely parallel those originally proposed by Munro (22). These are erotomanic, grandiose, jealous, persecutory, somatic, mixed, and unspecified types. However, other delusional themes are consistent with a diagnosis of delusional disorder as long as they meet the major defining criteria; in such cases, the mixed or the unspecified subtypes could apply.

Persecutory delusions may develop insidiously from a situation in which some degree of suspicion is justified. As the illness develops, the bounds of reason are exceeded, and simple suspiciousness is replaced by a delusional system. In time, the system becomes increasingly elaborate as more details are incorporated into it. The following case illustrates this development, as well as the preservation of affect leading the patient to act on the delusion.

8.5. Some Illustrative Cases

8.5.1. Case History 1: Persecutory Delusional Disorder

A 22-year-old single man, who lived on a farm with his parents, was brought to the hospital because of increasing suspiciousness of a neighbor. There had been long-standing friction between the patient's family and the neighbor, but over the preceding 3 weeks the patient had become convinced that the neighbor was involved in a grain and beef theft ring (which was indeed operating in the area) and informed the Federal Bureau of Investigation of his suspicions. He became convinced that his house was bugged and that some apples his father bought were poisoned because they had been purchased from a friend of the neighbor. He was hospitalized after he began sleeping with a gun for protection. On interview he was cooperative, although suspicious at times. His affect was appropriate to the delusional system. His speech was circumstantial and, at times, tangential when discussing the delusion. Over a 1-month hospitalization, the delusion cleared rapidly with antipsychotic medication, and at discharge he gained complete insight into the irrationality of his former beliefs. However, his suspiciousness toward the neighbor remained.

A. Meyer suggested the following states in the development of paranoid symptomatology (23). Meyer's stages started with 1) "a rigid makeup with a tendency to pride and self-contained haughtiness, mistrust and disdain," 2) "appearance of affectively charged dominant notions, as autochthonous ideas or revelation which illuminates all the brooding questioning in a manner to leave no need for further check," 3) "an irresistible need for working over the material for evidence to support the dominant notion. That it will support it is a foregone conclusion." 4) "Systematization of a sort that is so tightly knit that it remains logically correct if the original dominant notion be admitted." 5) "When the present has been ransacked for proofs and systematized, the attention is turned to the past with a re-examination of the past experiences in the light of newer certainty. There results misinterpretations of past events and retrospective falsification…" No psychiatrist has ever done a better job describing the march of circumstances in delusional disorder.

8.5.2. Case History 2: Jealous Delusional Disorder

A 35-year-old college man was brought to the hospital for threatening his wife with a hammer. She first became aware of his jealousy on their honeymoon, 3 years earlier, when he accused her of infidelity because she was not home on one occasion when he returned. Over the ensuing 3 years he often nagged her for confessions of past affairs. His bullying led to frequent arguments of such intensity that the police were once called. During the year before his admission, his suspicions had intensified to the

point that he accused her of having affairs after work whenever she was not home as promptly as he expected. He called her at work to check on her, set traps around the house, inspected her underwear, and even examined a vaginal smear under a microscope. He often kept her awake all night attempting to extract a confession of infidelity. His deteriorating work performance was blamed on his wife for the anguish she was causing him. He was hospitalized after the incident with the hammer and viewed the admission as an attempt by his wife and the doctors to "railroad" him and threatened to "even the score." On admission he was antagonistic and threatening, with a superior attitude. Although his speech was pressured, it was coherent. His affect was intense but appropriate to his suspicions. After his admission he became calmer, but the delusion remained unchanged during a 1-month hospitalization. He was discharged to another hospital, and his wife separated from him and subsequently obtained a divorce.

Delusional disorder with jealous delusions is referred to as *conjugal paranoia*, or as Othello syndrome, a reference to Shakespeare's famous character. Such patients become convinced that their spouses are unfaithful, and they become preoccupied with proving the infidelity and extracting a confession. Of all the paranoid disorders, these patients spend the greatest amount of time attempting to verify their suspicious thoughts (24).

8.5.3. Case History 3: Erotomania

A 47-year-old woman was convinced that her supervisor was in love with her, as she interpreted insignificant events as signs asking her to meet with him. After 3 years of such behavior, she had to leave her job on a sick leave. She was otherwise functioning well at work, had several friends and was fully functioning with regard to activities of daily living. She was treated with low-dose risperidone and cognitive-behavioral therapy (CBT). After a few sessions, she was offered a diagnosis and a case formulation based on CBT techniques as well as some basic psycho-education. She rapidly stopped seeing messages from her supervisor and developed full insight into her condition. After a year of complete symptomatic and functional recovery she returned to her job, and risperidone was slowly tapered down and discontinued. Psychotic symptoms relapsed a few months later but resolved when medication was reinstated and did not relapse over 6 years with continued medication. This case illustrates that with proper treatment, good outcome can be achieved in some delusional disorder patients.

Erotic delusional patients have delusions of secret suitors, and they interpret ordinary comments and gestures from the delusional suitor as concealed messages proclaiming their love. The "suitor" is often a prominent person with whom the patient has had some dealings. When their overtures are not reciprocated, these patients only become more convinced of the other's love for them, which, for various reasons, cannot be returned openly. Eventually, they may feel jilted and attempt to avenge themselves against their former "lover." This type of paranoid disorder has been referred to as de Clerambault's syndrome, after the French psychiatrist who formulated its original description, and is now called erotomania in DSM-5 (25–27).

8.5.4. Case History 4: Grandiose Delusional Disorder

A 56-year-old businessman developed diabetes 4 years before admission. Shortly thereafter, he developed his own treatment for the disease, which consisted of replacing sugar lost in the urine with a diet rich in sugar. He began publishing materials on his new treatment and advertised courses in it over the radio. Because he charged a nominal fee for these, he was arrested on charges of mail fraud and hospitalized for a court-ordered psychiatric examination. On admission he was cooperative and discussed his ideas with considerable loquacity and circumstantiality. His affect was appropriate to the ideas discussed. The delusional system remained fixed over a 3-week hospitalization, and he was discharged unimproved.

Patients with grandiose delusional disorder believe themselves to be persons of special importance. Common delusions of this genre include those of inventions and discoveries, as well as delusions of being an important part of an organization such as the Central Intelligence Agency. They can describe their delusions with such enthusiasm and loquacity that they may initially appear manic.

Patients with somatic delusional disorders are preoccupied with the appearance, odor, or function of their body (28). Common examples are delusions of body odor or halitosis. These patients are convinced of having a bad smell. Typically, they do not perceive the odor themselves, but they interpret benign remarks or nonverbal reactions as signs of disgust over the imagined odor. If the patient indeed smells an odor, this is a hallucination, and another disorder such as schizophrenia should be suspected. With delusions of infestation or parasitosis, the patient believes that he or she is infested with insects or parasites (Ekbom's syndrome) or other non-living (Morgellon's disease) foreign bodies under the skin (29). Patients with delusional hypochondriasis believe that they are affected by a serious illness and characteristically visit multiple physicians as well as other healers. However, since the inception of DSM-5, patients with fixed beliefs of delusional intensity about real or imagined defects in their appearance are diagnosed as having body dysmorphic disorder with absent insight/delusional beliefs, based on the research that suggested continuity between psychotic and non-psychotic presentations of these syndromes (9, 30).

DSM-IV would have diagnosed such patients with delusional disorder, somatic subtype; hence, a large part of the pre-DSM-5 literature on somatic delusional disorder may no longer apply, following this substantial revision. DSM-5 also includes a mixed subtype, which applies when no one of the above delusional themes predominates, and an unspecified type, which applies when the dominant delusional theme cannot be clearly determined, or is not described among the specific types.

8.6. Course

It is often stated that the typical course of delusional disorders is chronic with a very high degree of persistence of the delusions. It is difficult to provide reliable figures because of the high degree of heterogeneity among outcome studies. This can be explained by several factors related to sample composition, including differences in the proportion of subjects successfully followed-up, variations in case ascertainment methods, and the use of different diagnostic systems (31). Nevertheless, it is safe to say that there is no uniformity of outcome of delusional cases in any of these studies, i.e., there are broad variations regarding outcome, some being severely impaired, some achieving a very high level of recovery. Thus, this suggests that good outcome can be obtained in a significant proportion of delusional disorder patients (see clinical vignette 3 in section 8.5.3). However, the fact that delusional disorders, particularly jealous, persecutory, and erotomanic subtypes are not infrequent in forensic situations warrants careful risk assessment in such cases (32).

There are relatively few studies examining the issue of diagnostic stability over long periods of time. Available information suggests that in the majority of subjects, the diagnosis of delusional disorders is confirmed at follow-up but also that a significant proportion receives another diagnosis, most often schizophrenia (33).

8.7. Differential Diagnosis

Because delusional disorders are uncommon in clinical practice, the possibility that a delusional illness is caused by some other condition must always be kept in mind. A large number of causes are possible; these include mood disorders, schizophrenia and schizoaffective disorder, schizophreniform disorder, dementias, drug-induced psychoses, and neurological conditions that cause diffuse brain dysfunction (34).

Dementia may be accompanied by delusions and should be suspected in an elderly paranoid patient. Moreover, delusions may be a precursor of dementia. Indeed, in a study based on a Danish population registry, it was found that subjects receiving a diagnosis of delusional disorder performed after age 60 years had an eightfold risk of being diagnosed with dementia, compared to controls with osteoarthritis (35). Suspiciousness and delusional thinking can be more prominent than the cognitive impairment of the dementia, but the latter can usually be uncovered by a careful mental status examination. In questionable cases, psychometric testing should lead to the correct diagnosis. Delirium is characterized by a fluctuating state of consciousness, and the delusions are likewise evanescent and rapidly changing, while those of delusional disorders remain relatively fixed for the duration of the illness. In addition, the cognitive symptoms of delirium (e.g., disorientation and memory impairment) are absent in delusional disorders. Delusions due to other neurological conditions can present a greater diagnostic problem because of the absence of the cognitive impairment of delirium and dementia. For this reason, a careful medical history, with particular attention to the drug history, should be obtained, because delusions can be the result of a variety of medical illnesses and drug toxicities. These include pathology of the basal ganglia as in Huntington's disease and Wilson's disease, or of the limbic system involved in complex partial seizures or space occupying lesions. Other medical etiologies include autoimmune disease (e.g., lupus cerebritis), metabolic disease (e.g., porphyria, pernicious anemia), endocrine and infectious etiologies. Toxicity from substances of abuse such as central nervous system stimulants (e.g., amphetamines, cocaine) and prescription drugs (e.g., corticosteroids, L-dopa) can cause delusions as well. A urine drug screen is helpful in detecting surreptitious drug abuse.

Delusions are often the initial psychotic symptoms of schizophrenia. This diagnosis should be suspected whenever hallucinations are a prominent feature, the delusions tend toward bizarre, when the affect is blunted or inappropriate, when behavior is disturbed beyond direct consequences of the delusion, or when a thought disorder is prominent. If the correct diagnosis is schizophrenia, this will usually become apparent with the passage of time.

Mood disorder should be suspected whenever the delusional content is depressive or expansive, when a pre-existing mood illness is present, or when the family history is positive for one. The chronology of the delusions versus that of the depressive symptoms may help distinguish between a delusional depression and a delusional disorder complicated by a depressive syndrome. Since patients with delusional disorder have relatively preserved affect, they are often distressed by their delusions, and their clinical picture not uncommonly includes a depressive disorder. Examination of thought content may be helpful because prominent guilt, such as considering the delusional belief to be just punishment, militates toward a diagnosis of mood disorder. Grandiose and erotomanic delusions may be so expansive as to appear manic. In these subtypes the psychomotor symptoms of

mania are absent. Illness anxiety disorder (formerly hypochondriasis) differs from somatic delusional disorder in that the somatic concern is not centered around having a disease. Such patient suspects an illness and cannot be reassured by negative examinations but typically lacks the certainty of belief that is characteristic of somatic delusional disorders. Illness anxiety disorder patients may be characterized by poor insight to the extent that the patient fails to recognize that the concern is excessive and unreasonable, but these patients are never convinced beyond argument that they have a disease.

Paranoid personality disorder presents a diagnostic problem when the suspiciousness becomes so pronounced that it resembles a delusion. However, these patients are not truly delusional and are distinguished in this way from delusional disorders, although a person with a paranoid personality disorder may eventually become delusional, which would warrant a diagnosis of delusional disorder.

8.8. Laboratory Examinations

Several laboratory examinations are useful in ruling out other diseases that can present as a delusional disorder. Neuropsychological tests demonstrating cognitive dysfunction raise the possibility of a dementia or a psychotic disorder due to some other general neurological condition. A positive drug screen for amphetamines or other substances known to cause delusions raises the possibility of a substance-induced psychotic disorder.

8.9. Treatment

The medical evidence in support of drug treatment is based almost exclusively on case reports and series, with the exception of a few small, controlled trials of pimozide in delusional infestations. Munro and Mok (36) reviewed case reports published until 1994, totaling 208 patients who met DSM-IV criteria (for 75%, somatic subtype) and reported the majority of patients treated with pimozide experienced favorable treatment outcome, contrasting with a lower proportion of favorable outcome in those treated with other first-generation agents. Although pimozide has been, among first-generation antipsychotics, a preferred antipsychotic agent for delusional disorders, particularly the somatic subtype, there has been a steady trend toward treating delusional disorders with second generation antipsychotic agents. Indeed, a review of cases published since Munro's review until 2004 found a comparable proportion of favorable outcomes with second generation antipsychotics (37). However, as these are uncontrolled observations, drawn from unsystematic sampling, and apply mostly to somatic subtype of delusional cases, claims about the superiority of pimozide cannot be scientifically verified.

A few studies have outlined a particular cognitive style in delusional disorders [see above; (19)] which has stimulated interest in using cognitive behavioral therapy to treat delusional disorder patients, and successful applications of such therapy have been reported (38).

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9
Anxiety Disorders

Taylor C. Preston, M.D. and Richard C. Shelton, M.D.*

Abstract Anxiety is a common and normal phenomenon, involving multiple brain regions, including amygdala, locus ceruleus, and frontal cortex. Moreover, multiple brain transmitters regulate the presence and severity of anxiety; these include classical transmitters such as gamma aminobutyric acid, serotonin, and dopamine, as well as neuropeptides that include corticotrophin releasing hormone, substance P, neuropeptide Y, cholecystokinin, and vasopressin. Anxiety is highly adaptive, and involves both acute fear, related to an immediate threat, and anticipatory anxiety that is associated with possible future threat. Certain individuals are predisposed to develop anxiety disorders. Predisposing variables include both genetic factors (that may dispose toward anxious temperament), emotional traumas, and other psychologically mediated factors. Anxiety disorders represent a family of conditions with important distinguishing elements. Panic disorder and phobias involve reactions that are reminiscent of acute fear (albeit often worse). Specific and social phobias involve excessive fearful responses to identifiable things or circumstances in the environment. On the other hand, panic disorder is characterized by acute and intense fear responses that are not associated with a specific environmental cue, although people with this illness may experience aversive conditioning as a result of having spontaneous panic attacks in specific situations. Generalized anxiety disorder is a condition that, essentially, involves anticipatory fear (i.e., worry). Worries of everyday life are enhanced beyond any normal or adaptive functioning. Finally, acute stress disorder (ASD) and post-traumatic stress disorder (PTSD), while not technically classified as anxiety disorders, will be discussed in this chapter. These occur after a catastrophic, often life-threatening event. People with these conditions suffer persistent re-experiencing of the event (including intrusive thoughts or nightmares), avoidance of reminders of the event, and signs of increased arousal, such as difficulty sleeping, hypervigilance, or exaggerated startle response. Although complex, anxiety disorders are treatable conditions that respond to certain medications and specialized forms of psychotherapy.

Keywords Anxiety · Fear · Panic disorder · Social phobia · Specific phobia · Generalized anxiety disorder · Obsessive compulsive disorder · Acute stress disorder · Post-traumatic stress disorder · Antidepressants · Psychotherapy · Selective serotonin reuptake inhibitors

*This is a revised version of a previous chapter co-authored by Dr. A. Hunt.

T.C. Preston, M.D.
Assistant Professor, Department of Psychiatry and Behavioral Neurobiology,
The University of Alabama at Birmingham, Birmingham, AL, USA

R.C. Shelton, M.D. (✉)
Charles Byron Ireland Professor, Department of Psychiatry and Behavioral Neurobiology,
The University of Alabama at Birmingham, Birmingham, AL, USA
e-mail: rshelton@uab.edu

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9.1. Introduction

Anxiety disorders are common and often serious conditions, which are associated with considerable morbidity. For example, rates of disability with certain anxiety disorders such as panic disorder or post-traumatic stress disorder (PTSD) are high. As well, these conditions are commonly comorbid with other mental disorders such as depression and substance abuse disorders. This, in turn, is associated with an even greater risk of morbidity and mortality. For example, panic disorder associated with major depression has a much higher rate of suicide attempts than either disorder individually (1). However, early diagnosis and intervention will often lessen the overall severity and risk of these disorders.

Overall, the 12-month prevalence rate of having any anxiety disorder is about 12% and lifetime prevalence is nearly 20% (2). Specific and social phobias are the most common, with lifetime prevalence rates of 6.7 and 12.1%, respectively. Moreover, anxiety disorders are commonly comorbid with other psychiatric disorders, including major depression, dysthymia, personality disorders, substance abuse, or even other anxiety disorders.

9.1.1. The Neural Substrate of Anxiety

Anxiety, fear, aversion, and obsessive thinking are distinct symptomatic elements of anxiety disorders, but may reflect exaggerations of normal adaptive emotional responses. The most basic distinction in anxiety is between acute fear and anxious anticipation. Acute fear reflects the response to an acute threat, activating the "fight or flight" response, and involves activation of a number of brain regions, including locus ceruleus and amygdala (Fig. 9.1). The latter is involved in the encoding of fearful memory and, hence, aversive conditioning. Therefore, as well as being involved in acute fear, the amygdala is also intimately involved in negative anticipatory expectation; that is, anxiety (3, 4).

Acute fear activates the sympathetic nervous system, producing peripheral manifestations such as tachycardia, tachypnea, tremor, and diaphoresis. However, the perception of fear or anxiety involves the cortex, especially dorsolateral and orbital frontal regions. The cortex not only consciously registers fear, but also responds with survival behaviors. An important part of the connecting system between cortex and paralimbic structures is the cingulate gyrus, especially the anterior cingulate, which mediates the upward projection of fear- or anxiety-related information and downward regulatory signals, including both formal behavioral responses and more direct inhibitory activity. Hence, the frontal cortex and cingulate are significantly involved in the regulation of both emotional and behavioral response to fear-inducing stimuli.

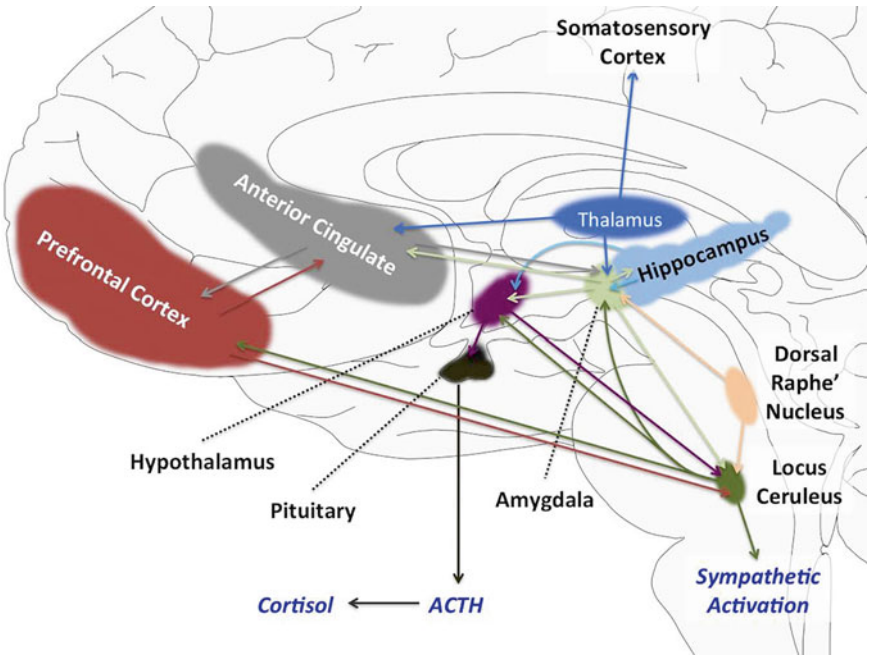

FIGURE 9.1. A simplified diagram of brain structures involved in the regulation of anxiety. Acute fear involves activation of both locus ceruleus and amygdala; the latter also plays a key role in memory encoding related to fearful stimuli. The frontal cortex is involved in both recognition of and complex behavioral responses to threatening cues. The anterior cingulate serves as a conduit of information between cortex and limbic structures, and serves a modulatory role as well. Serotonin, arising from the raphé nuclei, regulates activity in multiple brain areas.

The anxiety-related brain regions normally exist in a relatively quiescent or inhibited state. Redundant inhibitory systems such as those related to gamma aminobutyric acid (GABA) and serotonin modulate the responsiveness of this system. Additionally, neuropeptides such as corticotrophin releasing hormone, substance P, neuropeptide Y, cholecystokinin, and vasopressin, can have either activating or inhibiting effects. Therefore, this is a system that maintains a delicate balance of activation and inhibition. This balance maintains optimal responsiveness (a desirable feature in a stress—threat response apparatus) while also inhibiting anxiety and fear in non-threatening situations. Alternatively, perturbation of one or more of these modulators may induce or maintain anxiety disorders (5).

Pharmacological treatments for anxiety disorders typically activate or augment the natural neuronal inhibitory mechanisms. GABAergic drugs such as the benzodiazepines are a prime example. GABA receptors exist in a complex with chloride channels (6, 7). Chloride channels open in response to depolarization, propagating the action potential. By contrast, GABA receptors open chloride channels in a way that is not related to the propagation of action potentials, increasing the negative charge within neurons, and creating the inhibitory post-synaptic potential state. This inhibits subsequent action potentials until GABA is unbound and the chloride channels close, resulting in hyperpolarization. This decrease in neuronal firing appears to be related to the action of drugs that act on GABA receptors; GABA activation inhibits anxiety and can induce sleep. There are GABA potentiating drugs such as baclofen and gabapentin that exhibit anti-anxiety properties. However, they are not commonly prescribed for anxiety. Receptors for the benzodiazepine drugs such as diazepam and alprazolam exist in the same GABA-chloride channel complex. Benzodiazepines facilitate the action of GABA, which enhances and sustains the channels in the open position, producing a longer lasting effect than with GABA alone and, hence, reducing anxiety.

Serotonin from the raphé nuclei in the brainstem also serves an important regulatory role with regard to the structures that mediate anxiety. Serotonin is a complex transmitter in the CNS, with multiple receptor subtypes that can have opposing functions. However, the inhibition of amygdala activity appears to occur primarily via serotonin 1A receptors (8, 9). Therefore, drugs that enhance activation of this receptor will produce inhibition of amygdala activity. These would include inhibitors of the serotonin transporter (typically referred to as selective serotonin reuptake inhibitors [SSRIs]) such as sertraline and paroxetine, and the serotonin 1A partial agonist buspirone.

As noted earlier, activation of the locus ceruleus, located in the brain stem, is a significant mechanism mediating anxiety, and is thought to be an important brain structure in the generation of acute anxiety. Since anxiety disorders produce symptoms akin to acute anxiety, the locus ceruleus has been hypothesized to be important in the generation of panic attacks. SSRIs have an inhibiting effect on locus ceruleus firing, although only after chronic administration (typically 3 weeks) (10). The effect of serotonin at the locus ceruleus appears to be mediated via a different mechanism than in the amygdala. The serotonin 1A partial agonist buspirone actually enhances locus ceruleus firing activity (11, 12). This may be related to the relative lack of effect of buspirone in panic disorder (13) and reports of the drug actually inducing panic attacks (14, 15). Activation of the serotonin 2A type of receptors, on the other hand, inhibits locus ceruleus firing activity (12, 16). Therefore, the net effect of blocking the reuptake of serotonin is to inhibit both amygdala and locus ceruleus activity. This may explain the broad effects of SSRIs on different anxiety disorders.

9.1.2. Psychological Models

Behavioral models of conditioning and extinction help to explain the generation of fearful responses as well. A fear-inducing stimulus invokes the neural patterns of activation noted above, and also generates memory encoding of the event. With subsequent re-exposure to similar threatening stimuli, behavioral responses are produced more rapidly as a result of learning of the behavioral response repertoire. Repeated aversive stimuli result in a broader modification of behavior, such as inhibition of exploratory behavior in rodents, and sustained emotional activation (anticipatory anxiety). Long periods without exposure to the stimulus would normally result in an extinction of both negative emotions and anxiety-related behaviors. This, then, allows the brain to respond appropriately to an unpredictable environment.

In fact, any novel cue may invoke an initial anxious response. There appears to be a range of responsiveness of these systems between individuals, with some showing heightened reactivity to threat (real or anticipated) and novelty. In fact, behavioral inhibition, a temperamental dimension present in inhibition and characterized by withdrawal from novel environmental cues, appears to predispose to the subsequent development of certain anxiety disorders such as social anxiety disorder (17). Constructed more broadly, the anxious or emotionally reactive temperament seems to predispose to a range of anxiety and depressive disorders (18, 19). The apparent heritability of temperament, then, suggests that certain people are innately more reactive to real or anticipated threats and, therefore, are prone to the development of anxiety disorders.

A so-called tripartite model of mood and anxiety disorders was proposed more than 20 years ago (20–22). This reflects a tendency of symptoms of anxiety and depression, seen as a whole, to associate together in three, supraordinate clusters: negative affect (NA), reflecting a family of symptoms that includes rumination, worry, tension, and worry; positive affect (PA), which reflects the group of symptoms related to energy, interest, and motivation (or the relative lack thereof); and somatic anxi-

ety (SA), representing physical symptoms related to acute fear. As will be shown below, the NA axis tends to be elevated in all anxiety and mood disorders; that is, by definition, all these conditions share certain core distress symptoms. On the other hand, low PA is associated with the energy, interest, and motivation symptoms associated with depression, while most anxiety disorders do not have the same problem (23, 24). One exception is social anxiety disorder, in which PA tends to be low. This may reflect the propensity of people with social anxiety disorder to avoid enjoyable interactions with others. Therefore, the interest and motivation to engage with others may be absent because of the overriding anxiety of doing so. Finally, the SA dimension represents the physical symptoms of anxiety. This tends to be elevated in panic disorder (both during a panic attack and at other times), and in social and specific phobias on exposure to the feared stimulus. Therefore, the pattern of this symptom structure varies depending on the individual disorder.

As a result, there are both unique and shared features of anxiety disorders and mood disorders. Unfortunately, the current diagnostic schemes tend to include many of the symptoms common to the disorders; that is, symptoms associated with the NA dimension. Diagnosis will, then, be aided by focusing first on the unique elements of a specific condition. This would include the obsessions and compulsions of obsessive compulsive disorder (OCD), the low motivation associated with depression, and the somatic anxiety that occurs in a panic attack or, in the case of social and specific phobia, with exposure to a specific environmental cue. This leaves generalized anxiety disorder (GAD), which has substantial symptomatic overlap with other mood and anxiety disorders. GAD is a disorder of almost pure distress (i.e., NA), without strongly distinguishing features. However, as discussed more extensively below, GAD may, in actuality, be related to an anxious temperament and therefore tends to be a stable part of a person's life.

Anxiety disorders in general share certain common antecedents. Genetic factors appear to play a significant, albeit variable role in the genesis of these conditions. Described as so-called internalizing disorders, depressive and anxiety disorders share high rates of comorbidity, which may be accounted for by common genetic and environmental antecedents (25). One common factor appears to be related to temperament, a tendency for heightened negative emotional responses to environmental stressors (termed "neuroticism") (26). Temperament appears to have a significant genetic contribution, and the transmission of this trait is likely to increase the familial liability to this group of conditions.

9.2. Panic Disorder

9.2.1. Overview

The features of panic disorder are the presence of uncontrolled, recurrent, and unexpected attacks of severe anxiety along with the development of worries associated with the attacks, or avoidance of specific situations because of the attacks. Panic attacks are characterized by an abrupt surge of intense fear, together with symptoms of autonomic arousal (e.g., tachycardia and tachypnea), other anxiety symptoms (e.g., depersonalization), and a fear of losing control or dying. At least some of the attacks are unexpected and occur without exposure to phobic objects or situations. They may awaken a person from sleep, or be provoked by strong emotions, excitement or physical exertion. Other manifestations of the illness may include anticipatory anxiety and agoraphobia.

9.2.2. Criteria and Diagnosis

The panic attack can be thought of as an amplified form of what anyone might experience under conditions of acute threat, such as exposure to a deadly animal or a life-threatening accident, although without a clear provocation. As such, normal physiological responses such as rapid breathing or heart rate (with a feeling of chest tightness or discomfort) or tremor can become very severe. The hyperventilation, then, results in a rapid decline in CO_2, which causes vasoconstriction. This, in turn, is related to other symptoms of the attack, including numbness or paresthesias, dizziness or lightheadedness, chills, or the feeling of unreality (derealization) that comes with severe tachypnea. Because the symptoms are physical, unexpected, and not associated with a clear precipitant (at least during early attacks), affected persons can then interpret them as indicating some serious physical problems such as a myocardial infarction. As well, some feelings such as depersonalization or derealization may lead patients to believing that they are "going crazy" or "losing their mind." A full panic attack, then, is a catastrophic and often life-changing experience.

Affected persons will often seek help immediately by going to an emergency room or having an urgent visit with their physician. If the condition is recognized and treated quickly, the subsequent evolution of the condition can be truncated. However, if the panic attacks recur, people will often develop progressive avoidance of situations, culminating in agoraphobia, described below. Panic disorder is diagnosed after typical panic attacks followed by at least 1 month of one or more of the following:

- Persistent concern or worry about additional panic attacks or their consequences. As described below, this is often associated with avoidance behavior.
- A significant maladaptive change in behavior related to the attacks. A significant change in behavior: If panic attacks continue to occur, most people will develop altered behavior patterns, particularly avoidance of certain situations. When this becomes extensive, a diagnosis of agoraphobia is made.

Therefore, stated simply, panic disorder can be thought of as a condition in which recurring panic attacks are accompanied by either serious worry about the attacks or the development of avoidance behavior, or both. The occurrence of panic attacks and the persistent fears that accompany them can have a very adverse effect on daily life. Patients often find themselves unable to effectively engage in social, personal, or work related activities.

People with panic disorder may mistake the symptoms of panic or the more persistent anxiety that can develop along with panic disorder, as symptoms of a serious physical disease. Fears about dying from a myocardial infarction, cerebrovascular accident, or other serious condition, or a fear of becoming psychotic, often occur during attacks. However, worries about other serious conditions such as cancer, a neurological disorder, or other major medical condition, may develop over time. Patients may consult many health professionals and seek multiple medical tests because of the fears.

As with other psychiatric disorders, the diagnosis is excluded if the symptoms can be better accounted for by another psychiatric disorder (such as social anxiety disorder), a discrete medical condition (e.g., pheochromocytoma), or specific substances. This can be associated with the use of certain drugs of abuse such as cocaine. However, severe panic attacks may be precipitated by the use of marijuana or hallucinogens such as LSD or phencyclidine. People may also have severe anxiety symptoms that accompany withdrawal from alcohol or drugs, including sedative-hypnotics, benzodiazepines, or opiates.

9.2.3. Agoraphobia

In DSM-5, agoraphobia is formally defined as significant anxiety or fear about two or more situations such as being in open or enclosed places (27). Examples of commonly avoided situations include shopping malls, grocery stores, theaters, places of worship, or crowds of any kind. Exposure to these kinds of situations can lead to escalating anxiety that culminates in a panic attack. Anticipatory anxiety tends to build as the person approaches the feared situation or, with time, even thinks about it. This, then, functions like a negative reinforcement paradigm in which the avoidance is associated with a reduction in anxiety and is therefore reinforced. The individual fears or avoids these situations because of thoughts that escape might be difficult or help might not be available in the event of developing panic-like symptoms or other incapacitating or embarrassing symptoms. Forced exposure to feared situation almost always results in intense fear.

Unfortunately, the problem often builds over time and can become quite pervasive. Some people may become completely unable to leave their homes. If untreated, panic attacks and agoraphobia may result in progressive disability. As well, suicide can occur, especially when panic is accompanied by depression, which occurs in about 40% of untreated patients.

Agoraphobia may be diagnosed alone or as a comorbid condition with panic disorder or another psychiatric disorder. A diagnosis of agoraphobia alone usually occurs when there are relatively milder attacks or those with fewer than four of the typical panic attack symptoms. These more limited attacks may still lead to progressive agoraphobic avoidance, without a full panic attack meeting the four-symptom criterion in DSM-5. Very rarely, agoraphobic avoidance can develop without evidence of panic attacks at all; however, this is most commonly related to another disorder such as social anxiety disorder and would be diagnosed as such.

The relationship between panic attacks and agoraphobia often evolves in a predictable manner. Mild or limited symptom attacks are not rare in the general population, but often do not progress on to panic disorder or agoraphobia. However, in cases in which panic disorder or agoraphobia does develop, experience with recurrent panic attacks builds and patients will tend to progressively expand the scope of avoidance behavior. Subsequently, this tends to make recovery more difficult.

9.2.4. Epidemiology

As there is not yet new epidemiological data since the new DSM-5 criteria were released in 2013, available data reflect the DSM-IV diagnostic criteria (28). Epidemiological studies from 2006 suggest that the 1-year prevalence rates of panic disorder are 2.8% with the lifetime prevalence of 4.7% (29). Lifetime prevalence of agoraphobia without panic disorder was 0.8% (29). Certain factors tend to increase the risk for panic; these include female gender, being of Native American heritage, and being widowed, separated, or divorced. Panic attacks can occur across the lifespan, although the period of highest frequency tends to occur between about ages 25 and 45.

9.2.5. Etiology

9.2.5.1. Genetic and Biological Factors

Studies suggest that panic disorder is heritable, which contributes about 40% of the variance. Family studies have elucidated a relationship between genetics and the development of this disorder, with multiple studies demonstrating that first-degree relatives of panic disorder patients are more likely to also suffer from panic disorder in particular and anxiety disorders in general than the rest of the population. The genetic diathesis is also supported by twin studies which have shown that monozygotic twins have a higher concordance rate than dizygotic twins (45% vs. 15%) (30).

Multiple neurotransmitters have been implicated in panic disorder, particularly serotonin, norepinephrine, and GABA, all of which are found within the limbic system and cortex. This is based largely on the effectiveness of antidepressants (which act on serotonin and norepinephrine) and benzodiazepines (which interact with GABA receptors). This is further supported by data showing reductions in 5HT1A receptor concentration in panic disorder (31). Additionally, there are data to implicate the gene coding for COMT (catechol-O-methyltransferase), which is responsible for the metabolism of norepinephrine. However, the data are inconclusive (32).

Panic attacks themselves involve activation of cortical and subcortical regions. It should be noted that differences in the neural circuitry of patients with panic disorder have been identified. Decreased volumes of the temporal lobe and amygdala, as well as decreased cerebral glucose metabolism in the amygdala, hippocampus, thalamus, and brain stem have been found (32, 33).

Increased sympathetic activity is characteristic of the activation of panic attacks. At least during early attacks, the occurrence is abrupt, rising to the maxima within minutes, or usually within seconds. The initial upswing of physiological activation appears to occur via activation of the locus ceruleus, the principal source of norepinephrine in the central nervous system. Norepinephrine increases cortical arousal, and stimulates amygdala, hypothalamus, and other brain structures. Panic is associated with acute fear responses. This, in part, may be the result of a misinterpretation of the peripheral manifestations of autonomic arousal. Hence, norepinephrine projections directly activate the amygdala, generating an initial fear response. This, in turn, is reinforced by the interpretation of the signaling by the frontal cortex, which enhances the response. This latter mechanism is especially in force in subsequent panic attacks, which leads to further enhancement of the fearful response.

Therefore, peripheral symptoms of tachycardia, tachypnea, tremor, and diaphoresis are explainable by sympathetic outflow via the vagus nerve. However, a key symptom in a panic attack is hyperventilation. This, in turn, is responsible for some of the secondary features of panic attacks, such as dizziness or numbness and tingling of limbs or lips. This results from depletion of blood CO_2 and elevated O_2. In fact, one theory of the genesis of panic attacks suggests that brainstem sensitivity to CO_2 generates a false suffocation signal (34). This is supported by studies showing that breathing high concentrations of CO_2, or the infusion of sodium lactate (which increases central CO_2 levels), can potentially induce panic attacks. Moreover, panic attacks occur during sleep, typically in the transition from stage II to delta sleep, in which CO_2 concentrations may be high and O_2 relatively low (35).

9.2.5.2. Psychological Factors

Patients with panic disorder showed markedly anxious responses to the bodily cues associated with panic attacks. While anxious temperament or other cognitive predisposition may exist in people who develop panic, the exaggerated reactions to bodily sensations may be generated and are definitely reinforced by the panic attacks themselves. Panic attacks, then, can be seen as an aversive conditioning stimulus, leading to reinforcement of subsequent fearful responses. Patients can, then, become highly sensitized to physical cues such as rapid heart rate or shortness of breath that serve as reminders of panic symptoms, even if they are unrelated to a panic attack per se. In this case, the physical sensations are conditioned stimuli, which produce a conditioned response, generating a panic attack themselves.

Because the attacks generate such a fearful response, people will typically interpret them as indicating that there is a serious physical or mental problem. Both the experience of panic attacks in public places, and the anxious expectation of a panic attack occurring, will result in growing anxiety over time, yielding avoidance behavior. In fact, anxiety often builds as the person approaches the feared place. This, then, results in the physical cues that, as we have seen, can result in a panic attack. Therefore, anticipatory anxiety and avoidance behavior tend to build over time, culminating in agoraphobia.

From a developmental standpoint, panic disorder is more likely to arise with a backdrop of early adversity, particularly sexual abuse (36). This may account, in part, for the higher prevalence rate in women, since they are more likely to experience sexual abuse.

9.2.6. Differential Diagnosis and Comorbidity

Panic disorder is highly comorbid with mood and other anxiety disorders. Rates of major depression vary, but tend to be around 40%. However, these are not necessarily *co-occurring* conditions. That is, both conditions can occur independently over time.

Often, patients will suffer from panic disorder for an extended period before onset of depression, while depression pre-dates panic only occasionally. As well, depression can be a recurring condition in panic patients as it can be in persons without panic. Moreover, it is important to distinguish major depression from simple discouragement, unhappiness, or demoralization that are very common. Regardless, co-occurring depression or other mental disorders such as obsessive-compulsive disorder or personality disorder complicate the illness, making it more difficult to treat.

As with other mood and anxiety disorders, substance abuse rates are relatively high. As noted earlier, certain drugs such as cocaine (or other stimulants) or hallucinogens can precipitate anxiety or panic attacks; therefore, abuse of these drugs is uncommon. However, abuse of alcohol or sedative-hypnotics is relatively frequent, occurring in as many as 30% of patients. The use of benzodiazepines may also become problematic. However, in both instances, this tends to be the result of an attempt to control symptoms of anxiety, rather than a primary pattern of abuse. In many instances, patients will abuse substances such as alcohol for limited time periods, since the anti-anxiety effects of alcohol will wane over time. However, use of these substances is troublesome for a variety of reasons. For example, a pattern of escalating abuse will make withdrawal reactions more likely to occur. Withdrawal itself may be confused with panic, and panic attacks can occur in vulnerable people. In addition, although anxiety may be reduced immediately after the use of alcohol or sedatives, the anxiety may increase above the levels that would naturally occur as the drug clears. This, then, reinforces the behavior, which may result in addiction.

Any medical disorder may be concurrent with panic. Therefore, a good medical evaluation is imperative. Moreover, it is important to be aware that a very anxious patient may indeed be experiencing stroke or myocardial infarction. Note, however, that the features of panic are quite characteristic and, in most circumstances, not difficult to recognize if the clinician is sensitive to the possibility. There are specific distinguishing features with panic that are uncommon in other medical conditions. For example, depersonalization, derealization, or a fear of "going crazy" would not be common with other serious conditions such as MI. On the other side of things, persons who have had a heart attack complain of characteristic MI pain (e.g., radiating to the back, neck, or left arm). Persons with panic often describe a sense of chest "tightness" or "constriction" but seldom of "heaviness" in the chest that is more common with MI. Although stroke may result in numbness or paresthesias, unilateral muscle weakness does not typically occur in panic. A conservative approach to medical evaluation *is* warranted, and an electrocardiogram, exercise stress test, or MRI may be needed. However, be aware that persons with panic may request multiple medical tests as they seek an answer for their condition. An astute clinician should be able to recognize the features of panic disorder and, therefore, "give it a name," so to speak. This can be surprisingly reassuring for patients, and can avoid unnecessary medical expense.

Some medical illnesses can be precipitated by anxiety (e.g., unstable angina or asthma), while the course of others may be aggravated by anxiety (e.g., irritable bowel syndrome [IBS], migraine, or other pain). However, treatment planning will need to take these problems into account. Some can even affect the safety or efficacy of psychopharmacological treatments, such as certain cardiac conduction abnormalities, pulmonary, gastrointestinal or endocrine disorders, and pregnancy or lactation. For example, IBS can complicate treatment with serotonin selective reuptake inhibitors (SSRIs) since patients may be more sensitive than average to the lower gastrointestinal side effects that commonly occur with these drugs.

There are a few medical conditions that can mimic symptoms of panic. For example, pheochromocytoma, insulin- or serotonin-secreting tumors (e.g., carcinoid), or hormone-secreting small cell carcinoma of the lung may cause panic-like reactions to occur. There typically are concomitant features that distinguish these conditions. For example, pheochromocytoma results in a precipitous increase in blood pressure; this is uncommon in panic, and even when the blood pressure goes up, it is not as high. Insulinoma causes a marked drop in blood glucose, which does not occur in panic (although hypoglycemia may precipitate a panic attack). However, in the case of an insulin-secreting tumor, the blood glucose is very low. Although abdominal distress or diarrhea is common in panic, the propulsive diarrhea associated with carcinoid is not. Therefore, the differential diagnosis should not focus on signs and symptoms that are shared between conditions, but those that are unique to each.

Hyperthyroidism can tend to cause anxiety, including the physical symptoms associated with panic. However, these symptoms tend not to be acute and episodic as with panic. Other medical conditions that may cause anxiety or panic-like reactions include supraventricular tachycardia (or other arrhythmias), vestibular dysfunction (e.g., vertigo), or seizure disorders. The latter may be particularly hard to distinguish in the absence of generalized (i.e., tonic–clonic) seizures or loss of consciousness. In fact, certain seizures may cause episodes of anxiety with physical symptoms, and should be considered in the case of panic disorder that is difficult to treat, or when patients faint during a panic attack. Although the latter can occur, it is actually quite rare.

Acute hypoxia, such as that seen with pulmonary failure or an asthma attack, can mimic a panic attack. However, auscultation of the chest should yield an accurate assessment. As well, hypoglycemia, particularly if severe, can produce a panic-like reaction. However, blood testing for glucose can confirm that diagnosis.

Some of the most complicated management situations occur when serious medical problems happen in the context of panic disorder. For example, severe obstructive pulmonary disease is quite difficult; when the patient becomes short of breath, determining whether the problem is related to a panic attack, anticipatory anxiety, or the pulmonary illness itself (although this has been made less complex by the ready availability of pulse oximeters). Moreover, the low pO_2 and high pCO_2 may precipitate panic attacks.

As discussed below, people with panic tend to be quite sensitive to side effects of drugs. This occurs because of the fear of bodily sensations that plagues people with panic. Therefore, the natural physical side effects of drugs will precipitate anxiety and often result in the patient discontinuing or refusing the treatment.

Certain ongoing medical conditions may make the management of panic difficult. Obstructive pulmonary disease has already been mentioned. Unstable medical conditions like hyper- or hypothyroidism, angina, arrhythmias, or vestibular disease significantly interferes with the management of panic, and often those conditions must be treated before panic disorder can be dealt with successfully.

The extent of a medical work-up with a panic patient should be driven in large part by the differential diagnosis. That is, when panic occurs in the absence of evidence of other medical illnesses, then the medical evaluation should be truncated. It is good for the panic patient to receive a physical exam and standard annual laboratory tests with ECG, but this is simply consistent with good medical practice and can be done by the primary care physician (although a thyroid stimulating hormone evaluation is warranted if it is not routine with the PCP). Other laboratory tests should be kept to a minimum, unless there are other physical indicators. This will help to reduce the cost of care, but it also has another important effect. Although panic patients often want medical tests, a negative result is *not* reassuring, and may lead to more requests for testing. Actually, negative testing may actually *escalate* the anxiety, not reduce it. Although the psychological causes are complex, the patient may worry that they have an even more obscure and dangerous condition. The fear of an unknown but presumably serious medical condition can be quite severe.

9.2.7. Treatment

9.2.7.1. Pharmacological

Pharmacological treatment should be considered for most patients with panic disorder. The control of acute panic attacks and reduction of more general or anticipatory anxiety may speed recovery. Table 9.1 outlines common drugs with their daily dose ranges. While many medications are used to treat anxiety, they tend to fall into two basic categories: "antidepressants" with anti-panic properties and benzodiazepines.

9.2.7.1.1. Antidepressants

Of the medications that carry indications for the treatment of panic disorder, the selective serotonin reuptake inhibitors (SSRIs) are the most commonly used. Additionally, the serotonin norepinephrine reuptake inhibitor (SNRI) venlafaxine has been shown to be effective in panic disorder (37). Although certain drugs such as fluoxetine, paroxetine, and sertraline have been granted an indication for panic disorder by the US FDA, the therapeutic benefit seems to be a class effect for drugs that block the uptake of serotonin. SSRIs are first-line therapy because of their relative efficacy, tolerability, and lack of serious adverse effects. Occasionally, especially early in treatment, these drugs may acutely increase anxiety, and may also cause increased suicidal potential as a result. Therefore, patients should be closely monitored, especially at the start of treatment.

Other antidepressants, such as the tricyclics and monoamine oxidase inhibitors, are also quite effective in reducing panic. However, their side effect and safety profile make them quite difficult to use. Panic patients are very sensitive to side effects, and may not tolerate them. Moreover, the normal precautions associated with these drugs (discussed elsewhere in this volume) apply. In particular, the dietary restrictions of MAOIs must be strictly followed.

TABLE 9.1. Medications with FDA indications for panic disorder.

Medication	Starting dosage	Recommended daily dosage
SSRI		
• Paroxetine	10 mg daily	40–60 mg
• Fluoxetine	10 mg daily	20–60 mg
• Sertraline	25 mg daily	50–200 mg
SNRI/SSRI		
• Venlafaxine XR	37.5 mg daily	75–225 mg
• Duloxetine	20 mg daily	30–60 mg
Benzodiazepines		
• Alprazolam	0.5 mg tid[a]	0.5–2 mg tid[a]
• Alprazolam CR	0.5–1 mg daily	3–6 mg daily
• Clonazepam	0.25 mg bid[b]	0.5–2 mg bid[b]

Note that table applies to regular dosing in healthy adults. Pediatric and elderly dosing will be different, and may not be indicated.
[a]Three times per day.
[b]Twice per day.

Certain drugs may be less effective than would otherwise be expected. For example, although drugs that are potent norepinephrine reuptake inhibitors can eventually suppress panic, they tend to induce tremor, "jitteriness," and elevated heart rate. This, then, is anxiety provoking for patients and reduces tolerability. Such drugs would include certain tricyclics like desipramine. Furthermore, bupropion, which acts on pre-synaptic norepinephrine and dopamine, appears to be devoid of anti-panic properties. In addition, buspirone, which has anxiolytic properties for generalized anxiety (i.e., the "worry" type of anxiety), does not improve panic, and may actually worsen it. This probably has to do with the complex relationship between serotonin and anxiety regulation in the brain. Buspirone is a serotonin 1A partial agonist. Stimulation of these receptors actually increases the firing of the locus ceruleus, which is thought to underlie panic attacks.

Regardless of the antidepressant chosen, there are certain common principles to follow. Because of the sensitivity of panic patients to side effects, the adage to follow is "start low and go slow." That is, instead of beginning at a standard, antidepressant dose of a drug, start lower, and titrate the dose of the drug based on tolerability and efficacy. For example, sertraline is available in a 25 mg tablet. It is possible even to break that in half and start at only 12.5 mg. The dose, then, can be advanced in 12.5–25 mg increments every 1 or 2 weeks until panic suppression is achieved. This may ultimately require standard antidepressant doses (e.g., 50–150 mg/day). However, it takes time to achieve the maximum effect dose. Similarly, starting at 10–25 mg of a tricyclic like nortriptyline is appropriate, followed by increases in the same increments (i.e., 10–25 mg every 1–2 weeks) (38, 39).

The target for antidepressant treatment is complete suppression of panic attacks. This speeds recovery, allowing patients to resume a normal life. Although they may experience occasional, mild symptoms, major panic attacks should not occur. If they do, then the treatment is insufficient and should be adjusted accordingly.

The duration of treatment is indefinite, although many patients prefer to stay on the drug permanently for fear of a return of panic. Obviously, the drug is only effective while it is still taken, and panic may return on tapering or discontinuation, confirming the patient's fear. Therefore, antidepressant treatment is often a long-term proposition, which should be taken into consideration at initiation. For example, in a woman of reproductive potential, the prescribing clinician should discuss the pros and cons of treatment during pregnancy and lactation. Concerns have been raised regarding SSRIs and pregnancy because of the potential for birth defects including primary pulmonary hypertension (although a causal link has not been established) (40). As well, these drugs may result in discontinuation reactions in infants after delivery, which include respiratory distress, agitation, excessive crying, sleeping or feeding problems, or other difficulties (41). This may occur more often with short half-life drugs such as venlafaxine and paroxetine, although reactions with other drugs may occur. It should be noted, however, that findings have been inconsistent regarding effects of SSRIs on the children of mothers who took SSRIs during pregnancy. While Casper et al (42) found that children exposed to SSRIs in utero had no difference in IQ, language skills or temperament compared to controls, the same researchers found in a different cohort trial that children born to mothers on SSRIs during pregnancy had lower Apgar scores and scored lower on a psychomotor development index. Also, the clinician and patient must consider that uncontrolled panic attacks during pregnancy can be problematic, and may result in disability or even suicide. Moreover, the risk for cleft lip and palate and perinatal complications may be increased by panic disorder in the mother (43, 44). Therefore, the decision may not be a simple one.

9.2.7.1.2. Benzodiazepines

There are several possible uses for benzodiazepines in panic disorder. For example, relatively lower potency drugs such as oxazepam may be used on an as-needed basis early in treatment to both reduce initial anxiety and the anxious symptoms that can be induced by antidepressants. In this mode of treatment, the medications are used on an intermittent, as-needed basis, until the other treatments (e.g., antidepressant or cognitive behavioral therapy) take effect.

Higher potency benzodiazepines such as alprazolam and clonazepam are very effective to suppress panic attacks, and both have carried a US FDA indication for panic. The dosing range in clinical trials for alprazolam was 1–10 mg/day; however, typical amounts used in practice would range from 1 to 5 mg/day, in two or three divided doses. The dose of clonazepam for seizure disorders ranges as high as 20 mg per day. However, a more typical range for panic is 1–4 mg per day, divided. In both cases, the dose should be started low and titrated upward as needed. Beginning with 0.25–0.5 mg bid, the dose should be advanced within the dosing range in steps of 0.5–1.0 mg per week until either panic attacks are completely suppressed, or there are dose limiting side effects.

Common side effects with these benzodiazepines include excessive sedation and ataxia (clumsiness), which may be associated with an increased likelihood of motor vehicle or other accidents, or falls. Patients, then, must be warned about driving, operating machinery, or other activities requiring fine motor skills. Moreover, this class of drugs should not be combined with alcohol. Benzodiazepines interact with alcohol and increase the intoxicating effects. In severe cases, respiratory suppression can occur, although this is much more common with over dosage.

Uncommonly, unexpected emotional reactions to benzodiazepines can occur. For example, a small percentage of patients will experience a paradoxical increase in anxiety, which may be associated with irritability, agitation, and even combativeness. As well, a small number of patients may actually feel more depressed, and suicidal ideation may occur. In 2008, the FDA formally added a warning (short of a "black box" warning) regarding the increased risk of suicide for patients on clonazepam (and

other seizure medications) (45). Therefore, both the patient and, if possible, a significant other (e.g., a spouse or parent) should be warned of these effects.

However, the most serious concern about the use of benzodiazepines is dependency. Although the rate of true abuse of this class of drugs is relatively low, consistent use will produce physical dependency and a propensity to experience withdrawal reactions on abrupt discontinuation or reduction in dose. Withdrawal symptoms can include nausea, ataxia, dizziness, diaphoresis, anxiety, and elevated blood pressure. Abrupt discontinuation from higher doses may precipitate a seizure. As well, panic patients often experience marked worsening of anxiety with panic attacks on attempts to taper or discontinue the medications. This, in turn, can make these drugs very difficult to stop. For this reason, the potential for dependency and difficulty discontinuing should be explained to the patient before starting. For most patients with panic, the prescription of a high potency benzodiazepine to be used on a regular basis for panic suppression will lead to long-term use. Therefore, these drugs generally should be used as a last resort after other classes have been used.

9.2.7.2. Psychotherapy

A variety of therapies have been tested for panic, with varying success. Classical behavioral therapy, which includes graded exposure (discussed in detail below), can be helpful. The broadest evidence base supports the use of cognitive behavioral therapy (CBT) (46) and now there is also evidence to support the use of internet-based CBT (47). Additionally, there has been one randomized controlled trial supporting the use of panic-focused psychodynamic psychotherapy (48). It should be noted, however, that the comparison condition in that trial was applied relaxation training (another treatment without strong empirical evidence) and there was not a placebo (or equivalent) condition in the study. Other kinds of therapy have limited evidence supporting their usefulness in this condition.

CBT combines several components to manage the breadth of symptoms in panic disorder. For example, CBT incorporates classical behavioral therapy to deal with avoidance behavior. This involves graded re-exposure to the feared place or thing. This may begin with relaxation and guided visualization, leading ultimately to exposure to the situation in gradual steps. However, to get to this point, patients generally must deal with their exaggerated reactions to physical cues. These so-called catastrophic misinterpretations must be identified and confronted. This may require a process referred to as interoceptive exposure, in which physical sensations are generated by a variety of means (including caffeine or vigorous exercise). The therapist, then, will lead the patient through stages of correctly interpreting the physical sensations. This, over time, leads to extinction of the fears of inner stimuli. In turn, with gradual exposure to feared environments, the phobic anxiety can be extinguished (49, 50).

9.2.7.3. Course and Prognosis

The natural course of untreated disease is often chronic, and outcomes can be poor. Often, patients will see many professionals before arriving at an accurate diagnosis leading to effective treatment. This may be due, in part, to the difficulty in differentiating between panic attacks and other medical conditions. The delay in correct diagnosis can be catastrophic, with the development of progressive phobic avoidance. However, with early diagnosis and vigorous pharmacological and psychological treatment, most people have an excellent prognosis. Note that panic may be a recurring problem, although this may be reduced by the use of CBT.

9.3. Generalized Anxiety Disorder

9.3.1. Overview

An essential feature of generalized anxiety disorder (GAD) is unrealistic or excessive worry and apprehension about life circumstances. Sources of such worry can be varied but are often commonplace issues including health, finances, social acceptance, employment and job performance, family and marriage. This disorder may seem like a simple exaggeration of everyday concerns, but it is overshadowed by more severe tension, intrusive worries, anxious mood, and other symptoms. Comorbidity is common, and patients may suffer as "chronic worriers" without treatment. To meet DSM-5 criteria, the anxiety and worry should be present more days than not for at least 6 months, and the person should have difficulty controlling the worry.

The symptoms involved with GAD are both psychological and physical. Psychologically, the person with GAD can experience apprehension, anxiety, and hypervigilance. The latter reflects a propensity to mentally scan the environment to anticipate future stressors. In other words, the negative anticipation of the "next bad thing" is continually present. As well, people with GAD may startle easily and find themselves irritable and impatient. They often ruminate about potential unfortunate events, such as the death of a family member, financial disaster, social rejection, serious illness, or job termination. Even though the person may understand that the fears are unrealistic, the anxious preoccupation persists. Their concentration is often poor, and

some experience difficulty with memory. At night, their minds remain active so that they have difficulty in falling asleep, and when they fall asleep, they may do so in a fitful and interrupted manner.

There are multiple somatic symptoms that a patient may also experience, including muscular tension, aches, fatigue, increased agitation, irritability, restlessness, trembling, and difficulty relaxing. Signs of autonomic hyperactivity may also be present, including palpitations, sweating, hyperventilation with accompanying chest tightness, lightheadedness, and paresthesias. Gastrointestinal symptoms may also be present including abdominal distress, nausea, or diarrhea. Some patients may have increased urinary frequency. It may also affect their diet, with some people overeating and others restricting.

9.3.2. Diagnostic Criteria

Excessive worry is the hallmark of this GAD (27). In order to diagnose GAD, the symptoms must have persisted for at least 6 months. A person must experience multiple psychological and somatic symptoms during this time. These include muscle tension, restlessness, easy fatigue, difficulty concentrating, irritability, and sleep disturbances. While these symptoms can coexist with other disorders, the anxiety experienced must be distinguished from other DSM-5 disorders. For instance, the patient's anxiety and ruminations cannot be about having a panic attack as in panic disorder, social situations as in social anxiety disorder or obsessions as in OCD. Rather, the worries are about real life circumstances, albeit exaggerated. Another important feature of the diagnostic criteria is that the symptoms should cause significant distress and may impair everyday functioning. The symptoms should not merely be the result of effects of drugs or alcohol or general medical conditions that can present in the same way.

9.3.3. Epidemiology

Epidemiological data suggest that the 1-year prevalence rate of GAD is around 2.6%, with a lifetime prevalence rate of 6.2% (51). Since this condition may seem like normal worry, it is underdiagnosed. As with many other mood and anxiety disorders, women are more commonly affected than men. There is also a high comorbidity rate (50% or more) with depression and other anxiety disorders. Patients often present to primary care providers with either somatic complaints that are related to the underlying anxiety (e.g., insomnia or fatigue), or exaggerated concerns about their own health or that of significant others. Together, this leads to overuse of the medical system and frustration on the part of both patient and provider. Unfortunately, only about one quarter of patients are diagnosed.

9.3.4. Etiology

9.3.4.1. Genetics and Biological Factors

The propensity for GAD is at least partially heritable, with strong influence of environmental factors (52). The influence of environment may be either early adversity or recent stressors. However, GAD shows significant concordance with the features of the emotionally reactive temperament (also referred to as neuroticism) (53). Temperament is partially heritable and may serve as the foundation of risk for GAD (54). Moreover, the propensity for exaggerated emotional reactivity to exogenous stressors increases the propensity for major depression; this may explain the high concordance between GAD and depression (52, 55). In many, the GAD is the stable characteristic of personality, with intermittent episodes of depression related to recent stress. Therefore, the evidence of genetic risk, anxiety, and depression may reflect the interaction of genetically derived temperament and life adversity.

In fact, the distress-related symptoms of GAD are commonly found in other conditions (23, 24). Therefore, GAD has almost complete overlap with the symptoms of other mood and anxiety disorder. It is the specific symptoms of those disorders that distinguish them from GAD.

GAD shares symptoms with other anxiety disorders and involves similar neural substrates discussed earlier. For example, exposure to pictures of anxious faces heightens activity of the amygdala (56). Additionally, functional imaging studies have linked increased insular cortex activation to the brain's processing of affect, such as fear and sadness; it also affects how cognitive processing and behavioral responses are linked (57). Because GAD shares similar symptomology with other anxiety disorders, it should not be too surprising that similar neurochemical pathways and anatomical structures are involved as well.

Serotonin and GABA systems have been implicated in GAD; this may reflect more on the effects of psychotropic drugs than the actual causal dysregulation of brain function. As noted in the general discussion of the neural substrate, anxiety is a normal response to certain situations. It is regulated by many distributed and interacting brain systems, as well as the neurotransmitters serotonin, GABA, and others. Therefore, dysregulation in any of several different modulators of the anxiety apparatus may result in persistent anxiety symptoms.

9.3.4.2. Psychological Factors

The prominent psychological feature of GAD is the propensity toward anticipation of future negative events. This is coupled with playing out plans to respond to the potential events. Because the fears are exaggerated, the person spends a great deal of psychological energy in the constant "contingency planning." The question, then, is why does that occur in the first place?

As noted earlier, GAD appears to derive, in part, from temperamental features of high emotional reactivity to stress—either real or anticipated. This pattern of reactivity can be seen as an aversive conditioning paradigm. That is, in past adversity, the person experienced high anxiety that was difficult to control. This, then, represents a negative conditioning paradigm in which the person develops fears of possible future stressors. This becomes further reinforced in at least two ways. First, the worry itself causes distress, which heightens subsequent fear. However, occasionally the fear is realized, in which case future negative expectation is reinforced. Curiously, even though most fears do not come to pass, the occasional accurate prediction overrides extinction, and the worry persists.

This is matched with the anticipation that a future stress will be so bad that the person will not be able to handle it effectively. So, for example, a common fear is about the loss of a loved one—particularly a child being harmed or dying. The expectation is that the experience will be too great to bear.

There also is a kind of self-fulfilling nature to the problem as well. That is, that the fears lead to a modification of future behavior which may increase the likelihood of the event actually occurring. An example would be a person who fears abandonment by a girlfriend or boyfriend. The person may become obsessed with the person's fidelity, repeatedly challenging their faithfulness. Simultaneously, the person may engage in "clinging" behavior, such as insisting on constantly knowing the whereabouts of the other. This leads to frustration in the other person, and an eventual demise of the relationship. The fear, then, fulfills itself.

9.3.5. Treatment

9.3.5.1. Pharmacological

SSRIs or serotonin-norepinephrine reuptake inhibitors (SNRIs), are the most commonly prescribed psychotropics for the treatment of generalized anxiety disorder. People with GAD as a rule are not as sensitive to side effects as those with panic disorder. However, many of the same principles apply: first, start the dose relatively low, and, then, advance as required and tolerated. The notion is to reduce the anxiety to normal levels, allowing the person to live a normal life. The drugs approved for the treatment of GAD are listed in Table 9.2. While it should be noted that paroxetine and escitalopram are the only SSRIs with FDA indications for GAD, head-to-head randomized controlled trials (RCT) showed comparable efficacy between escitalopram, sertraline, and the SNRI venlafaxine XR (58).

Buspirone is a serotonin 1A receptor partial agonist, and has a moderate anti-anxiety effect (59). It is generally well tolerated and it has a low potential for sexual side effects. Furthermore, it does not have the potential for dependency or withdrawal reactions that plague benzodiazepines. Therefore, it is a good initial choice for patients with GAD.

A number of benzodiazepines have indications for GAD and, in fact, have quite potent anti-anxiety effects. However, as discussed with panic disorder, the effectiveness of benzodiazepines makes them highly reinforcing. Therefore, benzodiazepines have a high potential for dependency in this population. Low potency benzodiazepines may be used on an as-needed basis early in the course of treatment with SSRIs or SNRIs. However, generally, other treatments, including antidepressants, buspirone, or cognitive behavioral psychotherapy should be used prior to the regular use of benzodiazepines.

TABLE 9.2. Medications with FDA indications for generalized anxiety disorder.

Medication	Starting dosage	Recommended daily dosage
SSRIs		
• Paroxetine	10 mg daily	20–50 mg
• Citalopram	10 mg daily	10–40 mg
• Escitalopram	10 mg daily	10–20 mg
Buspirone	7.5 mg bid[a]	30–60 mg daily[b]
SSRI/SNRI		
• Venlafaxine XR	37.5 mg daily	75–225 mg
• Duloxetine	20 mg daily	30–60 mg

Note that table applies to regular adult dosing. Pediatric and geriatric dosing will be different, and may not be indicated.

[a]Twice per day.

[b]Usually given in a divided dose 15–30 mg twice per day.

β-Adrenergic agents such as propranolol have been used in the past to treat anxiety disorders. However, the effect is temporary and may facilitate the emergence of depression (60). Therefore, they should be avoided. Tricyclic antidepressants also are effective (61), but due to adverse side effects have given way to better tolerated agents such as the SSRIs.

Other antidepressants often tried in GAD include mirtazapine and bupropion. These are frequently used for patients who cannot tolerate the gastrointestinal or sexual side effects of SSRIs. There are currently no RCTs to support the treatment of GAD with mirtazapine (58), but there is one RCT supporting the efficacy of bupropion in GAD. Additionally, there is evidence to support the use of the anticonvulsant pregabalin, which has had 6 positive double blind RCTs supporting its use (58).

9.3.5.2. Psychological Treatment

Due to the complex environmental contribution in the development of GAD, psychoeducation and psychotherapy can prove helpful. Psychoeducation can identify lifestyle choices and life circumstances that can aggravate symptoms. For instance, many substances, such as caffeine, can lead to increased anxiety if consumed in large quantities. Various self-regulatory treatments such as biofeedback, relaxation, and meditation have been used with mixed results. However, cognitive behavioral therapy has the most evidence demonstrating its efficacy in treating generalized anxiety, and may be coupled with medication therapy (62). Techniques of cognitive therapy include cognitive restructuring; that is, improved reality testing in appraisal of risk. This can be coupled with improving problem-solving skills and relaxation techniques. There is preliminary evidence supporting mindfulness-based cognitive therapy for the treatment of GAD, but there has been no RCT yet to study this modality. This group therapy employs mindfulness meditation in a group setting and was shown to decrease both anxiety and depressive symptoms (63). While there is only one study regarding its use specifically in GAD, one meta-analysis of 39 different studies showed an effect size of 0.97 for the treatment of anxiety symptoms across an array of medical and psychiatric diagnoses (64). Other therapies have limited empirical support.

9.3.6. Differential Diagnosis and Comorbidity

The differential diagnosis of GAD includes an array of physical and psychiatric illnesses. In addition, there is a high degree of comorbidity with GAD and other disorders. Because of a high degree of concordance in symptoms between GAD and both mood and other anxiety disorders, care must be given to differentiate GAD from other disorders. This point is highlighted in the diagnostic criteria for generalized anxiety disorder.

GAD may accompany most any other psychiatric disorder, although it is most commonly associated with mood and other anxiety disorders. Anxiety symptoms are often prominent in patients with depression (e.g., anxious or agitated depression), making the differential diagnosis difficult. In fact, none of the symptoms of GAD are completely unique to the disorder. For example, patients with depression and other anxiety disorders can have negative rumination as a significant associated symptom. Therefore, making the distinction based on shared features is not an effective strategy. Knowing the distinguishing features of other disorders is a much better strategy. For example, patients with both GAD and major depression can have rumination, sleep disturbance, fatigue, poor concentration, and irritability. However, patients with GAD do not have prominent sadness, low motivation, guilt, or suicidal ideation in the absence of comorbid depression. These are features that help distinguish the diagnosis of major depression. Similarly, elements that distinguish anxiety disorders include "true" obsessions and compulsions (obsessive-compulsive disorder [OCD]), panic attacks (panic disorder), circumscribed fears (specific phobia and social anxiety disorder), and re-experiencing traumatic events (post-traumatic stress disorder [PTSD]).

Certain physical illnesses share features with GAD, which can prove problematic if they are not accurately ruled out or diagnosed. This would encompass hyperthyroidism (including Graves' Disease); associated symptoms include palpitations, insomnia, sweating, heat intolerance, increased appetite, diarrhea, tachycardia, tremor, weight loss, and warm, moist skin. Enlarged thyroid or exophthalmos may be present on physical exam. If a diagnosis of thyroid disease is suspected, thyroid function tests should be completed. Other medical illnesses can include angina or myocardial infarction, arrhythmias, Cushing's disease, obstructive sleep apnea, porphyria, and premenstrual dysphoric disorder. Many neurological diseases can have anxiety symptoms associated; this would include stroke, Parkinsonism, Alzheimer's Dementia, Lewy Body Disease, CNS infections (e.g., HIV), or other encephalopathies.

Substance use and withdrawal must also be considered with GAD. Substance-induced anxiety symptoms may appear with intoxication from many substances, such as caffeine, cocaine, amphetamine or other stimulants, hallucinogens, or marijuana. If the anxiety symptoms are substance-induced, they typically resolve after discontinuation of the offending substance. Withdrawal from alcohol, nicotine, benzodiazepines, or other sedatives may be anxiogenic. Many other medications also contribute to the development of anxiety, including sympathomimetics, aminophylline, prescribed stimulants (amphetamines or methylphenidate), levodopa, antihistamines, albuterol (and related drugs), steroids, metaclopramide, interferon, dopamine agonists (bromocriptine, pergolide, amantadine, levodopa), selegiline, and thyroid hormone preparations.

It is worth noting that withdrawal after discontinuation of alcohol, benzodiazepines, or other sedatives can be mistaken for generalized anxiety symptoms, and care should be made in differentiating substance related diagnoses due to potential significant adverse events—delirium tremens, seizure or death. Signs and symptoms of withdrawal can be very easy to misattribute, especially in patients in whom substance abuse is not suspected. This may be a particular issue with short acting drugs—including benzodiazepines such as alprazolam—that are taken on a regular basis. Moreover, inter-dose anxiety may be a particular problem with short half-life agents.

9.3.7. Course and Prognosis

Generalized anxiety disorder is a long-term condition. Prognosis, then, depends heavily on identification and therapeutic intervention. However, it is a treatable disorder with appropriate interventions, both pharmacological and psychotherapeutic.

9.4. Phobic Disorders: Specific Phobia and Social Anxiety Disorder

9.4.1. Overview and Presentation

Phobic disorders are characterized by intense fears of a circumscribed stimulus. In the case of specific phobia, the fear, aversion, and avoidance tend to be of things in the environment; for example, storms, animals or insects, heights, and the like. By contrast, social anxiety disorder is a type of fear that is confined to settings of social interactions. These would include speaking in public, eating in restaurants, and social interactions such as parties.

9.4.2. Specific Phobia

With specific phobia, the stimulus that causes anxiety may be an object or situation. Exposure to these things produces intense fear, anxiety, or feelings of aversion, leading a person to escape the situation or endure it with intense discomfort. The response is tantamount to a panic attack; however, with a phobia, the attack is in response to a specific stimulus, and is not spontaneous (although panic disorder may be superimposed on a long-term course of phobia). However, like panic, anticipatory anxiety and avoidance of feared situations may lead the person to modify his or her lifestyle.

Specific phobias are common and often do not affect a person's life in a major way. For example, a person with a spider phobia may avoid his attic or basement, but may not otherwise be seriously affected, unless exposed to an actual spider. In fact, a majority of affected persons never seek treatment. However, the person may have a substantial impairment. An example would be a person who fears enclosed spaces (claustrophobia) and completely avoids elevators. This may have an impact on their vocational choice or attainment.

9.4.2.1. Diagnostic Criteria

Diagnostically, this disorder differentiates from other anxiety disorders primarily because of a unique fear arising in very specific circumstances. In children, the fear or anxiety may be expressed by crying, tantrums, freezing, or clinging behavior. Confronting the phobic stimulus results in a strong sense of dread and often a desire to flee, and the person may experience physiological and somatic symptoms that are found in other anxiety disorders. Autonomic arousal may result in panic-like symptoms, such as trembling, shortness of breath, sweating, or tachycardia. Certain phobias (e.g., blood phobia) have been noted to have a sharp fall in blood pressure leading to dizziness and possible syncope (a "vasovagal" response). The fear or anxiety is clearly out of proportion to the actual danger posed by the object or situation. The diagnosis should be sensitive to the sociocultural context; the anxiety or fear should be excessive as compared to other members of the sociocultural group.

9.4.2.2. Epidemiology

Specific phobia is one of the most common disorders and may afflict up to 25% of the population with mild symptoms, although specific phobias meeting full diagnostic criteria have a 12- month prevalence of 7.1% and lifetime prevalence of 9.4%. There is increased risk of having this diagnosis in females and persons with low income (65). Onset of symptoms may occur in childhood, and commonly before adult life. Little is still known about the course of untreated specific phobias because phobias may resolve spontaneously or people learn to cope with these stressors, and may never come to attention.

9.4.2.3. Etiology

Little is known about the development of specific phobia from a biological or genetic standpoint. Little research has been done to isolate specific factors in the development of this disorder, both biological and otherwise. Observers have noted that specific phobia runs in families, and there may be a predisposition for family members of an afflicted patient to develop a phobia of the same type. As well, people with other anxiety disorders such as panic or social anxiety disorder may be at increased risk. There is research to suggest that evolutionarily relevant fears can occur without being learned by specific experiences (66, 67). Phobias generally do not occur as a result of a traumatic event. Although traumas may lead to phobic avoidance, this usually occurs in the context of traumatic stress disorders (see below). However, prior abuse or similar early traumas do not appear to predispose to phobias.

Specific phobia involves panic-like responses, and is thought to involve the same pathways as panic disorder (see above). Moreover, unlike spontaneously occurring panic, the phobic stimulus has to be first recognized, which then activates the neural response. Therefore, cortical activity is involved, as well as the amygdala and hippocampus. However, ultimately, midbrain structures, particularly the locus ceruleus, are likely to be involved.

9.4.2.4. Differential Diagnosis and Comorbidity

Comorbidity of other anxiety and depressive disorders is common in specific phobia, which may require treatment. However, care should be taken with regard to certain disorders. For example, people with psychotic disorders such as schizophrenia may have fears of circumscribed objects or situations. However, this kind of fear involves delusional thinking. As well, social anxiety disorder may result in fear and avoidance of certain circumstances that involve exposure to scrutiny by others, as described in greater detail below. With obsessive-compulsive disorder (OCD), the obsessional thinking or compulsive behavior may be stimulated by specific places or things, which then are avoided. As an example, people with OCD often avoid public restrooms because of a fear of contamination. Finally, simple phobias can cause extreme autonomic arousal similar to panic disorder, and may be mistaken for panic attacks. However, the recurring presence of specific stimuli will help differentiate between these two disorders. In fact, specific phobia is quite unlike panic in certain ways. People with phobias usually know precisely what they fear. Further, they seldom, if ever, fear becoming psychotic or having some serious medical illness such as a myocardial infarction. Specific phobias are typically easily recognized.

9.4.2.5. Treatment

No medications are indicated for the treatment of specific phobia. Drugs such as benzodiazepines may ameliorate symptoms, when the exposure can be anticipated. For example, people with a phobic reaction to blood may have high anxiety when blood is drawn. Likewise, people with claustrophobia may not be able to endure an MRI scan, because of being in an enclosed space. In these kinds of situations, a benzodiazepine can be used on an as-needed basis.

However, the treatment of choice for specific phobia is behavioral therapy, particularly exposure and desensitization. This kind of treatment often involves initial relaxation training, which then is followed by progressive exposure to the phobic stimulus. As an example, people with insect phobias might begin their treatment with looking at pictures of feared insects. They can progress to a plastic insect, and then, with time, to the actual insect. When done repeatedly, the fear is usually extinguished, and the phobia is no longer a problem.

9.4.2.6. Course and Prognosis

Phobias can develop throughout the life span. Phobias that develop in childhood may spontaneously remit later in life, although persistence is most common. As data suggests, many persons suffering from phobias will not present for treatment specifically for their phobia. Poorer outcomes have been associated with persons suffering from multiple phobias and lack of motivation or participation in therapy.

9.4.3. Social Anxiety Disorder

9.4.3.1. Overview and Presentation

Social anxiety disorder (previously referred to as social phobia) is defined as excessive fear of situations in which they may act in an anxious manner (e.g., have trembling hands) or otherwise show the anxiety and in which others might negatively evaluate them. They typically fear that they will or do something humiliating or embarrassing, which may lead to rejection or offense to others. This anxiety may be coupled together with a fear of being unable to avoid or escape certain situations. Many people experience fear or anxiety in almost all social situations. In children, the fear or anxiety may be expressed by crying, tantrums,

freezing, clinging, shrinking, or failing to speak in social situations. In social situations, people may experience anxiety that approaches the severity experienced in a panic attack. Consequently, the situations are either avoided or endured with intense discomfort. The presence of fear or anxiety is often not circumscribed to a single type of situation, and may extend to multiple social situations, even generalizing to all social interactions. This latter state is referred to as generalized social anxiety disorder, which may produce significant impairment.

A patient may experience fear when required to perform socially, such as speaking or performing publicly, participating in groups, or engaging in conversation. These kinds of fear are common, and may not meet full diagnostic criteria for social anxiety disorder. Other fears may involve more unusual situations. These can involve fears of eating in public, using public restrooms, or even writing while others are watching (for example, signing a check). Social anxiety disorder usually has a circumscribed fear of embarrassment. For example, although fear of writing may seem strange, the anxiety derives from a fear of appearing anxious, such as having shaking of the hands. Similarly, people often fear speaking in public because of a worry that they may exhibit the fear itself. People fear others' seeing their hands shake while speaking. Therefore, social anxiety disorder has a self-perpetuating characteristic. The symptoms associated with fear, such as shortness of breath, tachycardia, and tremor, actually aggravate the anxiety. This, subsequently, augments the anticipatory anxiety of other similar circumstances. The person often has had growing anxiety over time, which culminates in the actual experience. Showing anxiety, then, is inevitable.

9.4.3.2. Diagnostic Criteria

In social anxiety disorder, a person must show significant fear related to being exposed to scrutiny by others. People with this condition fear showing their anxiety and experiencing embarrassment. In other situations, people may fear saying something foolish, unintelligent, or embarrassing, and, therefore, avoid social interactions. There often is a history of avoiding social or performance situations, or enduring such situations with great distress. The fear often involves multiple areas of social interactions, and may result in significant impairment.

The fear is distressing and often causes significant problems in the person's life, interfering with multiple areas requiring social interactions. Although people may learn to "live around" the phobia, it often is at the price of educational or occupational attainment, or relationships. The symptoms are persistent, usually lasting at least 6 months (27). As in all disorders, social anxiety disorder must be distinguished from general medical conditions, the effects of substances, or other mental disorders.

9.4.3.3. Epidemiology

The 12-month prevalence of social anxiety disorder is 7.1%, while the lifetime prevalence rate is 12.1% (68). However, this may represent an underestimate, since mild symptoms are common. In the same epidemiological survey cited above, 24.1% of respondents reported at least one social fear during their lifetimes. Many people have significant fears of public speaking or being in public while engaging in various activities such as eating or writing, but only a small percentage of them meet full criteria for social anxiety disorder. This may be the result of having engaged in effective avoidance of the kinds of interaction that stimulate the fears. Females have a greater prevalence rate than males in the population, but an equal portion appear to present for treatment. The age of onset is usually during adolescence.

9.4.3.4. Etiology

Genetics and biology may play a significant role in the development of this disorder. One study, using neuroimaging, demonstrated increased reactivity in the amygdala in response to social cues (69). Abnormalities in the serotonergic and dopaminergic systems, as well as hyperreactivity of the autonomic nervous system in afflicted individuals have been noted (70, 71). Family and twin studies suggest that genetics contributes a moderate level of risk, and that the remainder of the risk is largely due to environmentally specific factors. As noted for other anxiety disorders, the emotionally reactive temperament appears to contribute significantly to the predisposition to phobias in general (26). Best-fit models support the notion that genetics, familial (i.e., "shared") environment, and individual-specific environmental factors contribute independent, but interacting, risk (72, 73).

There is also evidence to support that temperament and other factors such as cognitive distortions play a role in the development of social anxiety disorder, along with interaction with the environment. Children who have a first-degree relative with social anxiety disorder appear to be at a two- to threefold greater risk for developing social anxiety disorder than children who do not have a first-degree relative with this disorder. In addition, a mounting body of evidence implicates various neurobiological pathways in the development of this disorder, similar to those found in other anxiety disorders.

Social learning theorists have asserted that social anxiety can be "learned" through vicarious observation of others being humiliated in a social situation . Additionally, it has been found that patients diagnosed with social anxiety disorder are more likely to report that *their* parents avoided social interactions, suggesting that the modeling of social anxiety plays a role.

However, these theorists are quick to note that a temperament known as behavioral inhibition is thought to be the diathesis that separates persons who develop social anxiety disorder from those who do not, as certainly every person who has observed social adversity does not develop social anxiety disorder (74).

Classic behavioral theory posits that persisting fears may be associated with certain environmental stimuli (for example, a threatening animal), or that fears may develop in the context of pairing of a benign cue and another feared stimulus. The latter is a traditional view of "irrational phobias," that is, phobias of relatively neutral, non-threatening objects or situations. Although phobias may occur in the context of an adverse situation, traditional behavioral views have certain significant limitations. The fear of either an unconditioned (i.e., threatening) or conditioned stimulus (one that generates fear as a result of being paired with a conditioned cue) may certainly occur; however, the repeated presentation of the situation without threat typically results in extinction of the fear. This phenomenon, almost by definition, does not occur with phobic disorders. Therefore, although phobias may, on the surface, appear to correspond to a classical conditioning model, certain features are not consistent with this view. Therefore, sustained phobias are likely to arise from a mixed model, which may or may not depend on the presentation of an environmental threat.

9.4.3.5. Differential Diagnosis and Comorbidity

The diagnosis of social anxiety disorder requires differentiation from other similar appearing clinical pictures. The most significant differential is with other anxiety disorders. As already noted, interviewing to elicit specific features is most helpful. Although people with obsessive-compulsive disorder may avoid social situations, the reasons typically are clear. For example, they may have social avoidance because of a fear of contamination by exposure to others. Similarly, panic disorder often results in social avoidance, but in the context of a history of spontaneous panic attacks. Moreover, whereas both social anxiety disorder and panic disorder may share a fear of public embarrassment, the episodes of panic disorder are not context-specific—that is, they do not always occur on social exposure. People with post-traumatic stress disorder may have social anxiety and aversion, but this is specific to earlier trauma. For example, a woman who has been raped may carefully avoid situations in which she is exposed to men. However, the causal thread to the earlier trauma is usually clear.

Various personality disorders also may have a significant component of social avoidance. Patients with schizoid or schizotypal personality disorders may have little social interaction. However, their minimal social interaction is not the result of social anxiety per se, but rather is preferred by the individual. People with avoidant personality disorder also have social fears, including fears of embarrassment; however, this is a life-long and pervasive pattern. Of note, however, generalized social anxiety disorder is difficult to distinguish from avoidant personality and, in fact, may be the same condition, as both tend to be chronic and pervasive.

Psychotic disorders such as schizophrenia must also be considered. For example, psychotic patients may avoid social interaction, but because of specific, paranoid fears. They may, for example, fear that people are plotting harm against them, not simply that they might do something embarrassing. Moreover, the so-called negative symptoms of schizophrenia, which include apathy and social withdrawal, can result in similar avoidance. However, this occurs in the broader context of schizophrenia.

Social avoidance is seldom the result of the direct effects of substances (or withdrawal) or other general medical conditions. People with serious substance abuse may have relatively little social interaction. However, this is usually not the result of fear of embarrassment (although the physical consequences of substance abuse may make people want to avoid others).

9.4.3.6. Treatment

Both pharmacological and psychotherapeutic methods are useful in the treatment of social anxiety disorder. A number of drugs carry specific indications for its treatment. In particular, these include the SSRIs paroxetine and sertraline, as well as the SNRIs duloxetine and venlafaxine extended release. A summary of these medications along with their common dosages are found in Table 9.3. The doses used are similar to those used for major depression. The problem of increased anxiety early in treatment

TABLE 9.3. Medications with indications for social anxiety disorder.

Medication	Starting dosage	Recommended dosage
SSRIs		
• Paroxetine	10 mg daily	20–50 mg daily
• Paroxetine CR	12.5 mg	12.5–37.5 mg daily
• Sertraline	25 mg daily	50–200 mg daily
SSRI/SNRI		
• Venlafaxine XR	37.5–75 mg daily	75–225 mg daily

Note that table applies to regular adult dosing. Pediatric and elderly dosing will be different, and may not be indicated.

with SSRIs and SNRIs seen in panic disorder is not as prominent with social anxiety disorder. However, the principle is the same: start at a low dose and titrate upward until the desired result is achieved—that is, suppression of the social anxiety.

Other medications are also sometimes used in the treatment of the disorder. Benzodiazepines may be helpful when used on an as-needed basis; for example, people may take a relatively low dose of benzodiazepines such as lorazepam, clonazepam, or alprazolam in situations in which the feared social interactions cannot be avoided. This is often done prior to public speaking, for example. However, adverse reactions such as drowsiness or interference with recall may pose a problem. Therefore, the drug should be tested in a "non-demand" situation prior to being implemented. Note that many people have anxiety in multiple social situations, or may have unpredictable social interactions, making the use of benzodiazepines problematic. Due to the issue of dependence, benzodiazepines should generally be avoided for continuous use, particularly given the evidence of the effectiveness of SSRIs and SNRIs. Buspirone may also be effective in social anxiety disorder but the data are conflicting (58). Older drugs such as the monoamine oxidase inhibitors may also be effective, but are seldom used because of the risk of adverse events. Finally, drugs that block the autonomic arousal associated with social situations can also be used. Most particularly, this includes beta-blockers such as propranolol or atenolol, which can be used in anticipation of social exposure such as public speaking. As with benzodiazepines, beta-blockers should be tried prior to the social interaction because of the potential for side effects.

Traditional behavioral and cognitive behavioral therapy are effective. Both involve common elements, most particularly graded exposure to the feared stimulus. For example, a person with a severe fear of public speaking may begin by giving a speech alone to a mirror, followed by giving the speech to the therapist, then a small number of family and friends, a larger number of familiar people, and, eventually, working up to large groups of unfamiliar people.

Cognitive methods include elements such as reappraisal and hypothesis testing. Reappraisal involves actually addressing the negative thoughts associated with the fear, for example, that the person is likely to say something foolish or otherwise be noticed by others. Hypothesis testing may involve having the patient ask other people whether they noticed the symptoms of fear (such as shaking hands), or if the patient had said something foolish. These treatments are often quite effective in producing long-term improvement. In addition, the use of medications in the absence of behavioral methods is often only partially effective.

9.4.3.7. Course and Prognosis

The course of social anxiety disorder is typically chronic in the absence of specific treatment. Moreover, the chronicity may contribute significantly to social and occupational impairment. In addition, other comorbid mental disorders such as depression may contribute independent risk, worsening the overall course. It should be noted, however, that many people have mild symptoms without significant impairment.

9.5. Trauma-Related Disorders: Post-Traumatic Stress Disorder and Acute Stress Disorder

9.5.1. Overview and Presentation

Acute stress disorder (ASD) and post-traumatic stress disorder (PTSD) are conditions that are the result of exposure to extreme and emotionally traumatic events, typically involving a threat to life. Events such as war, torture, violent or sexual assaults, and natural disasters may predispose a person to developing these disorders. Of note, DSM-5 has added that the patient does not need to have been directly exposed to the trauma, but that they may have been traumatized by learning of something traumatic happening to a family member or friend (27). Also included are patients, such as emergency first responders, who have been repeatedly exposed to the horrific details of traumatic events, although this does not apply to exposure through electronic media, television, movies, or pictures, unless this exposure is work related. The majority of people do not experience lasting effects of exposure to severe threats; many develop acute stress disorder, only to recover completely. In the case of post-traumatic stress disorder, symptoms may manifest immediately or after months or even years after an event happens.

Acute stress disorder is very much like PTSD, and may be considered its precursor. However, most people who suffer from ASD will not necessarily develop PTSD, and not all people who develop PTSD initially had symptoms of acute stress disorder. However, ASD and PTSD have many common elements. ASD is diagnosed when symptoms are present for at least 3 days but not more than 1 month; beyond the month timeframe PTSD should be diagnosed.

9.5.2. Diagnosis

ASD and PTSD share many common characteristics, but have some key distinguishing features. Both of them require exposure to a traumatic event, most often one that involves a threat to their life or the lives of others. They have similar symptomology,

but the temporal onset and duration of symptoms distinguish them. ASD requires a minimum of 3 days from time of the trauma before the diagnosis can be considered. The reason for this is that the majority of people will have acute symptoms that resolve rapidly after exposure to such an event. By definition, ASD should abate within 1 month. Therefore, ASD serves as an intermediate disorder on a continuum between immediate stress reactions and PTSD, in which symptoms must be present for at least 1 month. If symptoms last longer than 6 months, then PTSD is considered chronic.

A formal diagnosis of ASD or PTSD requires that a person experience at least one extremely traumatic event, such as a life-threatening situation, serious injury, or a significant threat to well-being of the identified patient or other people. This involves the perception of an extreme threat, particularly of physical integrity. The person will have an extreme fear response to such an experience. Events commonly associated with development of these disorders include direct exposure to war or combat, torture, violent crime, sexual assault, and natural disasters. People who suffer from ASD or PTSD will continue to manifest significant emotional responses, which may be severe, after the event.

Diagnosing these disorders requires symptoms out of five concurrent ongoing sets of symptoms. First, the person must exhibit intrusion symptoms; that is, the person will relive events and feel as though they are actually happening again. This can include disturbing, intrusive recollections, dissociative events which are usually in the context of a reminder of the trauma, vivid dreams of the event, and visual, auditory, or other illusions that may elicit fear. Second, they may have a persistent inability to experience positive emotions (e.g., inability to experience happiness, satisfaction, or loving feelings). Third, patients may have dissociative symptoms, including derealization and an inability to remember aspects of the traumatic event (dissociative amnesia). Fourth, these experiences will result in avoidance of triggers for the anxiety—that is, reminders of the event. For example, combat survivors often avoid war movies. Fifth are arousal symptoms, the flood of intense feelings and experiences can be overwhelming for a person, and drive physiological arousal and activation. This can be exhibited as hypervigilance, exaggerated startle response, irritability, or difficulty sleeping. ASD can be diagnosed with the presence of any nine of the symptoms listed in DSM-5. For the diagnosis of PTSD, patients must have at least one symptom from all categories, intrusion symptoms, avoidance of stimuli, negative alterations in cognition and mood associated with the event(s), and alterations in arousal and reactivity. The requirement of experiencing negative alterations in cognition or mood is a category of symptoms that was newly added to the diagnostic criteria in DSM-5. This may include feelings of detachment or loss of interest in activities. The diagnosis of PTSD may also be accompanied with a specifier indicating the presence (or absence) of dissociative symptoms. The onset of symptoms may be significantly delayed in some patients; if the onset is delayed by at least 6 months, then the delayed expression specifier should be used. For a full list of symptoms, refer to the full diagnostic criteria in DSM-5, which also includes diagnostic criteria for children 6 years and younger. Note that the memories may manifest primarily in art or play in young children.

9.5.3. Epidemiology

The epidemiology of PTSD/ASD is directly associated with exposure to trauma. However, less than 10% of people exposed to trauma go on to meet full criteria for PTSD. The lifetime prevalence of PTSD in the US general population is around 6.8%, though rates are higher among women, children, and the elderly (75, 76). Many people who have been exposed to traumatic events may not meet full criteria for ASD or PTSD, but may have significant symptoms causing impairment or distress. In DSM-5, these can be classified as other or unspecified trauma-related disorders (27). Specific demographic groups are at a higher risk for ASD and PTSD. For instance, rates in war veterans are substantially higher than the general population. Similarly, refugees, survivors of concentrations camps, people who have been tortured, people with a history of early abuse, and those exposed to serious natural disasters are at high risk.

9.5.4. Etiology

The proximate cause of ASD and PTSD, the trauma itself, is clear. Unlike other anxiety disorders, these require an exposure to a specific environmental contributor (i.e., a significant traumatic event outside the range of normal experience). However, the stressor is, by itself, insufficient to cause traumatic stress disorders, as only a small proportion of people exposed to such stressors develop a full symptom picture. In addition, stressors that do not involve a direct threat to the person, such as divorce or the death of a loved one (with the exception of a traumatic death), do not typically cause ASD or PTSD.

Increased vulnerability to PTSD appears to be familial, and not due entirely to shared environmental factors such as abuse (77). Clearly, even with a genetic predisposition, the occurrence of ASD or PTSD requires traumas that are specific to an individual (77). Shared and non-shared environmental factors may be difficult to tease apart; for example, siblings may all experience abuse, while only one may have a subsequent life-threatening experience. Moreover, shared childhood environment should not be assumed in siblings raised in the same environment. Abuse or neglect may occur more with one child than another, depending on specific circumstances. One child may even be singled out for abuse, relatively sparing siblings. Of note, twin studies comparing PTSD in monozygotic and dizygotic twins demonstrated that PTSD is approximately 30% heritable (78).

Thus far, the candidate genes that have been postulated to have a role in PTSD have all been in the HPA axis, the locus ceruleus/noradrenergic system or the frontal/limbic system (78). Altered regulation of the hypothalamic–pituitary–adrenal (HPA) axis has been well studied in PTSD. Unlike what is seen in some patients with depression, this includes a relatively lower cortisol level and an enhanced feedback inhibition by cortisol (or analogs such as dexamethasone) (79). This, in turn, is consistent with the general inhibition or arousal associated with the condition. This pattern occurs in the case of PTSD related to recent traumas, but not in the context of prior traumas (such as remote abuse) (79). The opposite appears to emerge in the case of early trauma. In such cases, persistently elevated cortisol and blunted feedback suppression of the HPA axis is found, which is more like HPA axis abnormalities associated with depression. In either case, persistent dysregulation of the HPA axis appears to be significantly associated with PTSD.

Dysregulation of other neural systems has been postulated. For example, serotonin has a significant role in dampening stress responses, such as activation of the amygdala. Moreover, norepinephrine has a key role in mediating the enhanced central and peripheral arousal seen in these conditions. Further, neuropeptides that regulate these systems, such as corticotrophin releasing hormone, neuropeptide Y, and substance P (neurokinin) may be involved (80–82). However, the causal relationship is not clear.

Imaging studies suggest the involvement of specific brain regions in PTSD, particularly the hippocampus, amygdala, and frontal cortex (83). fMRI studies of exposure to reminders of the trauma suggest that the amygdala is hyperreactive. Further, the hippocampus often is reduced in volume (83), a phenomenon that may be associated with altered regulation of cortisol (84). Altered higher brain regulation of stress reactivity may be a consequence of trauma (83).

9.5.5. Differential Diagnosis and Comorbidity

The criteria for the diagnosis of ASD and PTSD are reasonably clear. However, care must be taken in making the diagnosis. PTSD-like symptoms may occur following a less severe trauma and, although this may be clinically meaningful, it does not meet criteria for diagnosis. In a related way, people with other anxiety or depressive disorders may have histories of serious trauma, including life-threatening events. Other conditions may share certain features with ASD and PTSD. For example, the insomnia associated with PTSD is found in many other conditions, such as major depression. Recurrent hyperarousal is present in other conditions such as panic or phobic disorders, and may even be present in OCD when the person is exposed to a stimulus that elicits obsessions (e.g., contamination). Moreover, PTSD is commonly associated with other DSM-5 disorders, such as major depression. However, since the treatment is quite different depending on the specific diagnosis or comorbid condition, accurate diagnosis, including recognition of comorbid conditions, is critical.

Psychotic disorders such as schizophrenia or delusional disorder may present after a significant trauma, since stressful events may precipitate acute psychosis. In fact, brief psychotic disorder may occur specifically after a serious trauma. In any psychotic condition, the content of the trauma may be incorporated into a delusional system, complicating diagnosis. Moreover, people with psychosis may have delusions about past traumas that did not occur and yet are firmly believed. Several factors, then, should be taken into consideration in the differential. It should be stressed that a psychotic diagnosis does not preclude the diagnosis of ASD or PTSD. However, in the presence of psychosis, consider several factors: 1) The plausibility of the story. 2) Proximity to the stressor—was the person actually present in the specified location at the time of traumatic event? 3) Corroboration by significant others, particularly family members. It is important to remember that corroboration may not be accurate either. The family member may believe the incorrect history, or they may deny an event that actually exists. Therefore, the whole picture has to be taken into context.

Another aspect to keep in mind is the possibility of factitious disorder or malingering. In factitious disorder, the symptoms are consciously fabricated in order to gain the sick role. As well, they may achieve attention, nurturance, and other desirable outcomes. However, in malingering, the exaggerated claims of injury (in this case PTSD) are still consciously fabricated, but occur as a result of a desire for compensation, to avoid prosecution for a crime, or to avoid work or other responsibilities. In other words, the patient is motivated by secondary gain. This may be difficult to distinguish from actual PTSD, since it may occur after a major trauma, and can co-occur with other symptoms or syndromes, such as depression or personality disorders.

Dissociative disorders can also be confused with PTSD. Dissociative conditions often occur after major traumas, especially childhood abuse. Although a dissociative event may occur on exposure to a reminder of a trauma, the person is often unaware of the event having occurred. Further, they may not exhibit other symptoms of PTSD, such as persistent hyperarousal, insomnia, or reliving the trauma.

Neither drugs nor medical conditions imitate the full syndrome of ASD or PTSD. However, medical illnesses or reactions to drugs (either acute effects or withdrawal) may occur in people who have had life-threatening traumas. These would be similar to those conditions that can cause panic type responses: pheochromocytoma or other hormone-secreting tumor, as well as alcohol or drug withdrawal.

9.5.6. Treatment

Treatment of ASD and PTSD depends on the severity and scope of symptoms, and usually requires a multifaceted approach including pharmacological, psychotherapeutic, and psychoeducational intervention, crisis management, and involvement of extended social support network such as family members, where possible.

At this time, two SSRIs—sertraline and paroxetine—carry an indication for treatment of PTSD and are considered first-line treatments for the disorder, although there is no reason to believe that the effect is limited to these two drugs. Recommended dosages are found in Table 9.4, though higher doses of these medications are often used. Medication management of ASD may simply be symptom focused, such as the temporary use of sedatives (e.g., zolpidem) or anti-anxiety drugs such as benzodiazepines. However, if the acute response is severe, or if more serious depression is comorbid, then an antidepressant is indicated.

Other medications have been studied, including the tricyclic antidepressants and MAO inhibitors, and have been found to be at least somewhat effective for PTSD. Atypical antipsychotics have shown promise for the treatment of moderate to severe PTSD, especially with concurrent psychosis; however, the evidence base is limited. Other medications are typically used to ameliorate specific symptoms of PTSD such as anxiety or insomnia. However, care must be exercised, especially with benzodiazepines, since co-occurring substance use disorders are common.

Many psychotherapeutic interventions have been tried, and a few seem to be effective. Probably the most effective approaches are trauma-focused CBT interventions, which typically involve exposure to the trauma using mental imagery, either in group or individual therapies. For example, uniform group therapies that bring together people with shared traumatic experiences appear quite effective. Effective therapies typically use exposure techniques such as exposing combat-related PTSD patients to sounds of gunfire in order to extinguish the associated fears. There is significant empirical support from controlled trials suggesting that these specialized forms of cognitive behavioral therapy are effective (85, 86). In addition, early aggressive treatment, particularly after the emergence of ASD, seems to help avert PTSD (87). For example, rapid interventions have been developed by the US military and others to avert combat-related PTSD. Particular techniques, such as exposure therapy, allow the patient to learn to confront and develop fear management strategies. However, patients may not tolerate re-experiencing, and high rates of dropout can be common. Therefore, management of factors, such as excessive anxiety, which may influence dropout, should be used.

One treatment method for trauma-related mental disorders is Eye Movement Desensitization and Reprocessing (EMDR). This method couples specific eye movement exercises with trauma-focused psychotherapy. Although there is some evidence indicating benefit, most studies of this method have had small sample sizes, often without adequate blinding, and without a placebo-equivalent condition. They also have not controlled for "allegiance effects"—that is, the comparison treatments have been delivered by EMDR adherents. Moreover, the specific eye movements that are thought to be an essential part of the treatment may not be necessary to achieve positive results (88), although this remains controversial (89). Therefore, the existing data should be interpreted with caution (90).

9.5.7. Clinical Course and Prognosis

The onset of acute stress disorder will be associated with recent trauma events. The course of acute stress disorder is self-limited, with symptoms lasting no longer than 4 weeks, though it may evolve into a more chronic pattern of symptomology. The onset of PTSD symptoms may occur at any time during the life of an individual. Delayed onset of symptoms after trauma can make predicting who will experience symptomology difficult, and many persons may have a subclinical presentation.

TABLE 9.4. Medications with indications for post-traumatic stress disorder.

Medication	Starting dosage	Recommended daily dosage
SSRIs/SNRI		
• Escitalopram	10 mg daily	20 mg
• Fluvoxamine	50 mg daily	50–300 mg
• Fluoxetine	20 mg daily	20–80 mg
• Paroxetine	10 mg daily	20–50 mg
• Sertraline	25 mg daily	50–200 mg
• Venlafaxine XR	75 mg	75–225 mg
Benzodiazepines		
• Alprazolam	0.5 mg tid	0.5–2 mg tid
• Clonazepam	0.25 mg bid	0.5–2 mg bid

Note that table applies to regular adult dosing. Pediatric and elderly dosing will be different, and may not be indicated.

Full recovery is variable, and may or may not be dependent on treatment. There are instances of spontaneous remission without treatment, with estimates at about 30%. Approximately one third never fully recover despite interventions. Many people suffering from PTSD will continue having mild to moderate symptoms despite treatment. The average time until significant recovery is 24–36 months with treatment and 64 months without. A more favorable prognosis is associated with rapid onset and short duration of symptoms, good premorbid functioning, and strong social support systems.

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10
Obsessive Compulsive Disorder

Tanya K. Murphy, M.D., S. Evelyn Stewart, M.D., and Demian Obregon, M.D.

Abstract OCD is the fourth most common neuropsychiatric disorder with lifetime prevalence estimates of 0.4–3.5%. Family and twin studies suggest a strong genetic component, and molecular genetic studies are being carried out to identify genes contributing risk to OCD. It is postulated as a frontal-striatal disorder and functional neuroimaging studies provide a strong support for the dysfunction of cortico-striatal-thalamic-cortical neurocircuit. OCD can be secondary to a variety of medical conditions that range from deteriorative neurological illness, to head injury, and to autoimmune disorders. Few reports and no controlled studies exist in the treatment of acquired/secondary OCD. Both CBT and pharmacotherapy are effective first-line treatment modalities for OCD. Brain stimulation and/or psychosurgery have been tried with varying success in treatment of refractory OCD. Environmental, genetic, and clinical factors interact in a complex fashion in the individual patient. This chapter will examine OCD from the medical perspective.

Keywords Obsessive compulsive disorder · Cortical-striatal-thalamo-cortical circuit · Genetics · Neuroimaging · Autoimmune · Treatment

10.1. Introduction

As defined in DSM-5, obsessive compulsive disorder (OCD) is characterized by obsessions (recurrent, unwanted, and distressing thoughts, images, or impulses) and/or compulsions (complex, repetitive, rule-governed behaviors that the patient feels driven to perform). Patients usually try to actively dismiss obsessions or neutralize them by seeking reassurance, avoiding situational triggers, or engaging in compulsions. Obsessions and compulsions are maladaptive, and lead to impaired functioning. They typically center on four themes: contamination, sexual/aggressive/checking, and ordering and symmetry. Common compulsions include excessive cleaning, checking behaviors, ordering and arranging rituals, counting, and repeating routine activities. Compulsions usually involve observable behaviors (e.g., hand-washing) but may also consist of covert mental rituals (e.g., counting, or ritualized performance of mental math). Symptom themes can vary over the course of the illness but those without a personal or family history of tics are more likely to have more frequent contamination themes. In

T.K. Murphy, M.D. (✉)
Maurice A. and Thelma P. Rothman Chair of Developmental Pediatrics, Director, Rothman Center for Pediatric Neuropsychiatry, Professor, Departments of Pediatrics and Psychiatry and Behavioral Neurosciences, Rothman Center for Neuropsychiatry, Department of Psychiatry, University of South Florida, St. Petersburg, FL, USA
e-mail: tmurphy@health.usf.edu

S.E. Stewart, M.D.
Director, Pediatric OCD Program, Associate Professor of Psychiatry, University of British Columbia, Vancouver, British Columbia, Canada
Senior Clinician Scientist, Child and Family Research Institute, Vancouver, British Columbia, Canada
e-mail: evelyn.stewart@ubc.ca

D. Obregon, M.D.
Department of Psychiatry and Behavioral Neurosciences, University of South Florida,
USF Health, Morsani College of Medicine, St. Petersburg, FL, USA
e-mail: dobregon@health.usf.edu

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the DSM-5, hoarding has been categorized as a distinct disorder, and is no longer considered a specific form of OCD. The addition of a separate diagnosis is supported by extensive research suggesting that, although the two disorders can co-occur, patients with symptoms of hoarding have a number of significant phenomenological differences than those with OCD, including distinct cognitive processes, reinforcement patterns, and response to treatments commonly used to address symptoms of OCD (1).

The proposed lifetime prevalence of OCD in the pediatric and adult population ranges from 0.4 to 3.5% in national and international epidemiological samples (2–7). Approximately half of all OCD patients first present in childhood, before age 15 (8) with biphasic symptom presentation (9) of around age 10 and then again in early adulthood with males presenting with an earlier onset. In adulthood, the proportion of affected males and females is about equal. In clinical samples, OCD appears more common in Caucasians than African-Americans. However, epidemiological data are conflicting with one study suggesting no differences in prevalence as a function of ethnicity or geographic region (10) and another suggesting that the prevalence of OCD is significantly lower in African-Americans and Hispanic-Americans compared to Caucasians (11). Minorities, particularly African-Americans, are often under-represented in research studies on OCD (12). It is unclear whether recruitment efforts geared to African-Americans have been inadequate (e.g., not culturally sensitive) or that the prevalence of OCD is actually lower in this population. One study suggests a later age of OCD onset in African and Caribbean Americans (13).

The clinical course of OCD is often described as chronic and unremitting. The proportion of patients having chronic course has been reported in a range of 44–84% (14, 15), while the proportion of patients having an episodic OCD was observed only in 5–10% (15, 16). That some cases of OCD can show an episodic course is less well recognized (17). In studies on the course of OCD in children and adolescents, the rate of symptom remission is not uncommon but still represents a minority of cases. In a 2-year follow-up study of a community-based adolescent cohort, the remission rate was 69% (18); however, in studies of clinical adolescents, the majority had some symptoms and remained on medication 2–7 years later (19–21). Factors that contribute to a more benign course include the presence of precipitating event, episodic nature of the symptoms, and good social/occupational adjustment (22, 23). Factors that contribute to a more disabling, chronic course include early age of onset, presence of tics, comorbid major depressive disorder, parental psychopathology, poor response to medication, severe OCD symptoms at onset, and poor insight (15, 20, 23, 24). Once OCD becomes entrenched in the daily lives of those affected (due to the patient's social adaptation to time-consuming rituals and intrusive thoughts), the illness often becomes chronic and disabling.

Evolution acts to conserve normal behaviors in both animals and humans. One way is by "hard wiring" fixed, repetitive behaviors such as grooming, nesting, harm avoidance, reproduction, maternal bonding, and all the behaviors essential to the propagation of the species. A number of mechanisms and contributions (i.e., stress, illness, and genetic predisposition) can disinhibit or overactivate these fixed, repetitive behaviors leading to OCD (19), to the degree that functionality is impaired. Obsessional thoughts centered on the loved one are proposed to contribute to the social networks needed for the maintenance of the human race (25). Preservation of neurohormonally induced behaviors is postulated as the common pathway between humans and animals. Specific neuropeptides are essential to memory acquisition and maintenance or retrieval of behavior sequences in the grooming, maternal, sexual, and aggression categories (26, 27).

10.2. Neuroanatomical Features of OCD: The Basal Ganglia

OCD is postulated as one of the frontal-striatal disorders, which include a variety of neuropsychiatric disorders, such as tic disorder, Tourette's syndrome (TS), body dysmorphic disorder (BDD), and trichotillomania (28). A characteristic of this group of disorders is a complex interaction between the exogenous and endogenous stimuli and the neural systems that link stimuli to cognitive and behavioral responses. The basal ganglia serves as an important node in a complex system of parallel, segregated and somatotopically organized cortical-striatal-thalamo-cortical (CSTC) loops that integrate motor and cognitive functions. Inputs flow from the cortex to the basal ganglia through the globus pallidus internus (GP_i) and substantia nigra pars reticulata (SN_r) to thalamus and, in turn, back to cortex. Projections from a specific region of motor cortex synapse with neurons in the caudate and putamen, which in turn project to the internal segment of the globus pallidus and substantia nigra, pars reticulata, whence axons arise and project to the thalamus, and from thalamus back to the same cortical region. Cognitive and emotional processes are handled by CSTC loops which project from associational and limbic areas to the striatum, particularly the ventral striatum or nucleus accumbens (NAc). The ventral striatum serves a critical role in the integration of emotional and cognitive behaviors and is thus highly relevant to OCD. Other models of OCD incorporate other frontal circuits including the dorsolateral prefrontal cortical-parietal network involved in executive planning, orbitofrontal as well as anterior cingulate cortices (29). Neuroimaging studies support the dysfunction of CSTC neurocircuit in OCD (30) and further implicate deficits in feedback inhibition circuits from dorsolateral prefrontal cortical-parietal network coupled with possible hyperactivation of orbital frontal and anterior cingulate cortices (31).

10.3. Neuropsychiatric Disorders Frequently Comorbid with OCD

In early onset OCD, comorbid psychiatric disorders are present in about 80% of the cases. Major depression is seen in approximately 66%, attention deficit hyperactivity disorder (ADHD), oppositional defiant disorder (ODD), or multiple anxiety disorders in 50% and enuresis or speech and language disorders in 33% (32). Tics often develop during the course of OCD in childhood, if they are not present at the time of symptom onset. In the presence of tics, obsessions often involve violent or sexual themes, or focus on symmetry and compulsions involve checking, counting, repeating, touching, or "evening up" (i.e., to make items or actions symmetrical or even on each side) (33). In adults, lifetime comorbidity of major depression is reported in a range of 32–78% and the comorbidity of other anxiety disorders, such as specific phobia, panic disorder, generalized anxiety disorder, and social phobia ranges in 14–54% (34). Interestingly, OCD is frequently comorbid with schizophrenia. The OCD comorbidity rate was 14% in a study of patients with first episode of schizophrenia, which had less potential of confounding effects, such as medication-induced OCD (35). This high level of comorbidity (that is more evident in early onset OCD) suggests that the underlying relationship between OCD and other disorders is nonspecific or is due to overlapping neurophysiology of central nervous system (CNS) dysfunction.

10.4. Genetics of OCD

Although exact pathophysiologic mechanisms remain elusive, the importance of genetic contributions to OCD etiology has been supported by numerous lines of research. Using family and twin study methodology, the long-standing observation that OCD "runs in families" has been empirically confirmed. Moreover, given remarkable advances in technology over the past few decades, the search for OCD genes and mechanisms of inheritance has involved thousands of OCD subjects and utilized segregation analyses, linkage, candidate gene studies, and genome-wide association study methodologies.

Family and twin studies provided substantial evidence for genetic factors in predisposing individuals to OCD. Several family studies reported a higher rate of OCD and subthreshold obsessive compulsive symptoms (OCS) among the first-degree relatives of persons with OCD (36). First-degree relatives of OCD probands were approximately six times more likely to have OCD, compared to control relatives, and OCD was more common in relatives of probands with early age of onset, compared with adult onset probands (37–40). A meta-analysis of data from five family studies with OCD probands revealed a summary odds ratio (OR) of 4.0 (95% CI: 2.2–7.1) for OCD in the first-degree relatives (41). The unadjusted aggregate risk based on 1,209 total first-degree relatives of OCD probands equals 8.2% versus 2.0% in 746 control relatives (42). Increased rates of tics among first-degree relatives of OCD probands (43) as well as increased rates of OCD among first-degree relatives of TS probands (44) suggest some cases of OCD may share components of the same genetic origin as tic disorders (43, 44). Interestingly, the younger age-at-onset of OCD symptoms and possibly male gender were associated with increased tic disorders in relatives.

Since Lange published the first cases of twins with OCD in 1929 (45, 46), numerous twin studies have shown elevated concordance (80–87%) among monozygotic (MZ) twin pairs compared with dizygotic (DZ) twin pairs (47–50%) (47, 48). The heritability estimates were 44% for obsessive–compulsive traits and 47% for obsessive–compulsive symptoms in a study with 419 twin pairs (49). Moreover in children, estimated heritability rates for obsessive–compulsive symptoms from other studies were even higher, ranging between 45 and 65% (45).

Several complex segregation analyses were performed to investigate the mode of inheritance for OCD. The results supported the existence of genes that have major effects on the transmission of OCD (50–52). A complex segregation analysis of OCD in 153 families (80 case and 73 control families) found evidence consistent with involvement of a dominant or co-dominant gene or genes of major effect, especially in families ascertained through a female proband (39). A recent study of 52 families (35 cases and 17 controls) ascertained through pediatric probands also revealed a major susceptibility locus when age-at-onset was incorporated into the model (40). However, Mendelian factors only partially explained the familial aggregation of the phenotype and residual familial effects were necessary to adequately fit the data, which implied that polygenic factors may also contribute to the etiology of OCD (39, 40).

Because of the strong genetic component involved in OCD, there have been efforts to identify the susceptibility genes by means of whole genome linkage analyses, candidate gene studies, and a genome-wide association study. Several genome-wide linkage scans of OCD have been published, which aimed to narrow down regions of the genome that may be responsible for genetic vulnerability in OCD-affected families (53, 54). In the first genome-wide linkage scan (53), seven pedigrees (56 subjects) containing pediatric probands with OCD and at least two affected relatives were genotyped, the initial findings on 2q, 9p, and 16q were followed up by genotyping additional markers in the original subjects plus ten additional family members. The strongest finding was on 9p24, which originally had a dominant parametric LOD score of 2.25 at D9S288. This finding on 9p was supported by the Johns Hopkins group in a follow-up linkage study targeting this region (55). Interestingly, a glutamate transporter gene (*SLC1A1*) that encodes excitatory amino acid transporter 3 (EAAT3) resides in this 9p24 chromosomal region,

and several groups reported an association between this gene and OCD (56–59). Most recently, a meta-analysis of SLC1A1 found only weak associations between OCD and a single nucleotide polymorphism (SNP) rs301443 in the overall sample and between OCD and SNP rs12682807 in males-only, neither of which maintained significance following correction for multiple testing (59). The second genome-wide scan was performed in 219 families at an approximate density of 9 cM, and found suggestive signals from chromosomes 3q27–28, 7p, 1q, 15q, and 6q (54). In a similar study of Costa Rican families, chromosome 15q14 (LOD 3.13) was identified (60, 61).

Over 80 candidate gene studies of OCD have been published (36). These have focused primarily on the serotonergic and dopaminergic system-related genes, such as serotonin receptor/transporter, dopamine receptor/transporter, Catechol-O-Methyltransferase (COMT), and Monoamine Oxidase A (MAO-A) genes. For the serotonin system, serotonin 1B receptor (*5HT1B*), serotonin 2A receptor (*5HT2A*), serotonin transporter (*SLC6A4*), and Tryptophan hydroxylase 1 (*TPH1*) were studied for association; and except for *5HT2A*, negative results outweighed positive findings (62–70). The dopamine receptor types 2, 3, and 4 (*DRD2*, *DRD3* and *DRD4*) and dopamine transporter (*DAT1*) genes were investigated (71–73), and the positive association was only replicated for a 48-bp repeat in exon 3 of DRD4 (71–74). For COMT, Val158Met polymorphism has been studied by several groups using both case-control and family-based association methods, with mixed results (42). Finally, two groups have reported an association between MAO-A gene (65, 75) and OCD. Interestingly, they also found sexually dimorphic effect of MAO-A on genetic susceptibility to OCD. As mentioned above, an association between a glutamate transporter gene that encodes EAAT3 (*SLC1A1*) and OCD was reported by several independent groups (56–59), although a meta-analysis of these data did not identify significant association (59). Glutamate system genes warrant further investigation as functional candidates for OCD, based on multiple lines of evidence, including: 1) elevated glutamate levels in brain regions within OCD patients in magnetic resonance spectroscopy studies (76–78); 2) corticostriatal glutamatergic mediation of stereotypic behavior in mice (79) and results of glutamate modulating agent augmentation studies in OCD (80, 81). However, sample sizes in OCD candidate gene studies to date have resulted in low power to reliably detect significant association.

The existing animal models of OCD, such as the Sapap3 mutant mouse (82), Hoxb8^{lox} mutant mouse (83), DAT1 knock-out mouse (70), and 5-HT$_{2C}$ receptor knock-out mouse (84), may be very useful in identifying specific genes and neurobiologic pathways involved in the pathogenesis of OCD. However, the question whether the behavior is a direct result of the specific gene or caused by the other downstream events may still remain (85). Moreover, significant limitations exist with respect to identifying an animal phenotype for obsessions, which comprise a major component of this disorder's symptomatology.

Finally, the first genome-wide association study of common SNPs in OCD examined data from 400 OCD-affected probands and their parents, 1,465 OCD-affected cases and 5,557 ancestrally matched controls. The strongest p-value (3.84×10^{-8}) was found for SNP rs6131295 near BTBD3 (broad complex tramtrack bric a brac domain containing 3), a common structural domain within proteins, although this did not meet the threshold for genome-wide significance ($p < 5 \times 10^{-8}$). Of interest, significant enrichment of frontal lobe expression quantitative trait loci (eQTLs) was observed among the most strongly associated SNPs (86).

In summary, family and twin study data support the familial aggregation of OCD, particularly in early-onset cases. Segregation analyses implied a major gene effect. However, genome-wide linkage and association studies have not confirmed any susceptibility locus, probably due to phenotypic and genetic heterogeneity. A number of candidate gene studies were conducted for association, with mixed results. Several lines of evidence support further investigation of glutamate system-related genes as candidates for OCD. A better understanding of environmental triggers, OCD subtypes, comorbid tic disorders, OCD pathophysiology, and further development of animal models may ultimately lead to locating genes that confer risk to OCD (87). Lastly, much larger sample sizes and collaboration across international OCD research centers will be required to achieve this goal.

10.5. Neuroimaging Studies

Although not always consistent, structural MRI brain imaging studies have suggested basal ganglia and frontal pathology, such as reduced volume of bilateral orbitofrontal cortices and amygdala, absence of the normal hemispheric asymmetry of the hippocampus–amygdala complex, and decreased caudate volume in patients with OCD (88–91). In studies investigating brain structures in medication-naïve children with OCD, significantly smaller striatal volume, larger ventricle, and larger corpus callosum were observed (92, 93). In addition, the size of corpus callosum was correlated significantly with OCD symptom severity, and age-related increase in callosal size seen in normal subjects was absent in OCD patients (93). The significance of corpus callosum differences in OCD was further supported by case reports of OCD patients with hypoplasia of the corpus callosum (94) and small anterior and posterior callosal regions compared to healthy control subjects (95). Further evidence of connectivity abnormalities in OCD is suggested by conflicting findings of reduced fractional anisotropy in cingulate, parietal, and right occipital areas versus increased fractional anisotropy observed in right medial frontal, left cingulate bundle, and internal capsule regions by diffusion tensor imaging (96–98). Moreover, greater number of subcortical hyperintensities are seen by T_2-weighted MRIs suggestive of microvascular pathology (99); whereas smaller pituitary volumes implicate hypothalamic-pituitary-adrenal (HPA) axis dysregulation (100, 101).

Functional neuroimaging studies also revealed dysfunction or increased activity in the corticostriatal pathways in individuals with OCD (102). In addition, OCD patients appear to preferentially activate bilateral medial temporal structures (typically used for conscious, explicit information processing) instead of the striatum during implicit sequence learning tasks in a PET study, which also support the corticostriatal dysfunction in OCD (77).

Several functional neuroimaging experiments using a symptom provocation paradigm or the use of cognitive-behavioral probes of corticostriatal circuitry and limbic (amygdala) circuitry to study changes of brain activities in individuals with OCD found activation of isocortical, paralimbic (medial orbital gyrus, anterior cingulate, temporal cortex, and insular cortex), limbic (amygdala), and striatal (caudate and lenticulate) areas in association with OCD symptoms (29, 103). Similarly, adults and children with OCD displayed deficits in cognitive flexibility and decreased fronto-striatal activation by fMRI (104, 105). Connectivity studies using resting-state fMRI suggest poor connectivity in frontal-striatal-thalamic circuits in youth with OCD in contrast to excessive connectivity in areas implicated in emotional processing (dorsal striatum/medial prefrontal cortex connections) in youth and adults with OCD (106).

The neural correlates of OCD symptom dimensions have been examined using functional neuroimaging techniques (28, 107). For example, cerebral blood flow in the striatum was increased with checking symptoms and decreased with symmetry/ordering symptoms, while washing symptoms correlated with increased cerebral blood flow in bilateral anterior cingulate and left orbitofrontal cortex in a study using fMRI (108). In another study using fMRI with symptom provocation paradigm, bilateral ventromedial prefrontal regions and right caudate nucleus correlated with washing; putamen/globus pallidus, thalamus, and dorsal cortical areas with checking; left precentral gyrus and right orbitofrontal cortex with hoarding; and left occipitotemporal regions with aversive, symptom-unrelated provocation (109). A small study of pediatric OCD found reduced activity in the right insula, putamen, thalamus, dorsolateral prefrontal cortex, and left orbitofrontal cortex during contamination symptoms provocation whereas lower activity was observed in right insula and thalamus in symmetry provocation experiments using fMRI (28, 110).

Also neuroimaging studies suggest that right hemisphere structures are more frequently or more dramatically involved than the left hemisphere (111–113). In several studies reporting neurological examination findings, subtle left hemibody signs and dyskinesias (fragmented movements) in both children and adults were detected, suggesting more prominent right than left hemisphere involvement (114–116).

In summary, structural neuroimaging studies have been inconsistent; however, functional neuroimaging studies have provided a strong support for a subtle developmental brain anomaly and altered function in the CSTC circuitry. The preliminary data from functional neuroimaging studies with or without a symptom provocation paradigm suggested different OCD symptom dimensions may be mediated by distinct, albeit partially overlapping, neural systems (28, 117).

10.6. Neuropsychologic Studies

Characteristics of OCD such as doubting, overvalued ideas, and perfectionism may have a neuropsychological basis. Studies of neuropsychological function in OCD have suggested deficits in executive function, attention, set-shifting and manipulating spatial information in adult patients. Adult research also suggests that OCD symptoms influence problem-solving efficiency (related to speed) rather than accuracy. For example, when performing on the Wisconsin Card Sorting Test (a set-shifting task), one study found that patients with OCD required significantly more trials, besides making more perseverative and other errors than controls (118) whereas another study showed no differences (119) suggesting these findings may relate more to the symptoms rather than vice versa. However, another study found first-degree relatives of those with OCD shared similar impairments in neurocognitive domains of delayed verbal recall, set-shifting, response inhibition, and visuoconstructive abilities compared to controls implicating these specific domains of executive functioning as endophenotypes for OCD (120). Another study also showed impairment in set-shifting, response inhibition but intact short-term memory (digit span, etc.) (121).

Reduced verbal and design fluency in patients with OCD was found when compared to controls, with evidence of a correlation between severity of OCD symptoms and design fluency (122). Additionally, patients with OCD may have non-verbal and praxic memory deficits, which may represent the cognitive substrate of doubt-related phenomena such as checking (123). In a review by Olley, Malhi, and Sachdev (124), it was proposed that OCD patients have a selective deficit in learning new task rules on the basis of external feedback. Other research shows a selective deficit of OCD patients in associative learning tasks (125). Reward processing is largely dependent on ventral striatal-orbitofrontal circuitry and brain imaging studies in OCD have consistently shown abnormal activation within this circuitry. Figee et al. (126) compared brain activity during anticipation and receipt of a reward between patients with OCD and healthy controls, using a monetary incentive delay task and fMRI. Patients with OCD showed attenuated reward anticipation activity in the nucleus accumbens compared to healthy control subjects.

Neuropsychological studies have revealed impaired visuospatial processing, deficits that are consistent with right frontal-subcortical dysfunction. Studies have shown poor performance on the Rey-Osterreith Complex Figure Test (ROCFT) suggesting deficits in non-verbal memory (127, 128) perhaps based on poor strategy selection in reproducing the figure (127). This

interaction between deficits in organizational strategies and memory problems when tasks require implicit organizational strategy (i.e., effort to recall unstructured information) may have contributions to doubting. Children with OCD have shown similar neurocognitive profiles albeit much fewer studies exist. Marked impairment in visuospatial recall memory (as assessed using the ROCFT) was observed in spite of average to above-average performance on academic and other neurocognitive measures. Those with elevated streptococcal antibodies fared worse on executive function measures (129). However, discrepant findings have been reported both in the pediatric and the adult literature suggesting that few differences exist between patients with OCD and carefully matched controls on an array of neuropsychological tests (130–132). Heterogeneity in presentation may be explained by environmental and genetic variations. For example, BDNF Val66Met polymorphism which attenuates BDNF activity does not appear to be a risk factor for OCD but the presence of a BDNF Met allele may be associated with a poorer executive functioning in OCD (133).

10.7. OCD Induced by Psychological Trauma

Early stressful events (trauma, disruption of social environment secondary to moves, illnesses, etc.) have been associated with the onset of OCD in some cases (134). Over 50% of children and adolescents cite a precipitating event (135). Prolonged exposure to stress and trauma are theorized to increase the hypersensitivity to perceived threats leading to OCD symptoms (136, 137). The relationship between OCD and post-traumatic stress disorder (PTSD) found in clinical samples is likely due to symptom overlap between the disorders (137) as well as comorbid depression (138) but post-traumatic OCD may differ in specific clinical features (139–141) and cognitive domains (142). Individuals with hoarding were more likely than those with OCD but without hoarding to have a history of a traumatic experience (143).

10.8. Structural Brain Etiologies of Obsessive Compulsive Disorder

Clear and mounting evidence suggests that abnormalities in the orbitofrontal cortex, basal ganglia, thalamus, and the interconnecting pathways are responsible for the symptom presentation of OCD. Given these anatomical associations, it would logically follow that structural insults to these areas could precipitate OCD symptoms. Although there have been few studies to systematically study these relationships, there are a growing number of case reports and case series showing that there are, indeed, sporadic acquired cases of OCD that result from insults to these brain areas. Cases of damage to frontal-subcortical structures have been shown to be the result of epilepsy, traumatic brain injury (TBI), strokes, tumors, carbon monoxide poisoning, wasp sting necrosis, and manganese intoxication (144–148). Other progressive neurological disorders that affect components of frontal-subcortical circuits (e.g., postencephalitic Parkinson's disease, neuroacanthocytosis, progressive supranuclear palsy, and Huntington's disease) also can present with OCD symptoms (146). While the symptom presentation in these cases is similar to idiopathic OCD, because they are caused by a secondary condition, they are classified in the DSM-5 as "Obsessive-compulsive and related disorder due to another medical condition (state medical condition) with specifier OCD-like symptoms due to another medical condition."

The rate of onset of OCD following traumatic brain injury is unknown, although previous reports have placed the incidence at between 0.5 and 7.8% of brain injuries (149). Although symptoms that would meet full diagnostic criteria of OCD are relatively uncommon following TBI, it has been well documented that up to 30% of all brain-injured patients will develop anxiety-spectrum disorders including generalized anxiety disorder, specific phobias, panic disorder, and stress disorders (149). The emergence of other psychiatric disorders is common as well. In one study examining the new onset of psychiatric disorders in children following TBI, it was revealed that 76% of the subjects developed a new psychiatric disorder within 2 years of a head injury (150). In this particular study, one of the 50 patients with TBI went on to develop OCD (a rate of 2%) (150). Although it was once thought that long-term psychiatric and neurocognitive sequelae occur only with moderate or severe brain injuries, more recent evidence indicates that significant psychiatric sequelae including OCD can occur even in mild TBI (150, 151) and without any evidence of abnormalities on MRI or CT scans (152–154).

The incidence of new-onset OCD symptoms following other brain insults including tumors and strokes is unknown. Given the relatively few numbers of cases reported in the literature, it is likely that the rates are very low. The scant literature describing OCD symptoms following carbon monoxide poisoning, Huntington's disease, Parkinson's disease, and other causes of acquired OCD, also points to the likelihood that the overall incidence of secondary OCD due to neurological disease is very low. In all cases of acquired OCD, it is implied that the immediate cause of the OCD symptoms is the insult itself. In cases where acquired OCD presents in the elderly population, it becomes more likely that there is an underlying medical cause for the OCD symptoms, as the rates of idiopathic OCD decline with advancing age (155) and rates of strokes and tumors increase. Given this shift in risk, some have argued that it is prudent to pursue a medical workup including brain imaging when new-onset OCD symptoms occur after age 60 (156).

Brain damage from TBI is often diffuse or involves multiple areas of the brain. The most common areas of brain involvement in secondary OCD involve the frontal, temporal and cingulate cortices, the basal ganglia, or the interconnecting areas (145, 157–161). Corresponding SPECT data reveals areas of hyper-or hypoperfusion reflecting changes in function in these brain areas (145). Similarly, in studies that show clear structural damage to single or multiple areas, corresponding SPECT studies show more extensive areas with abnormal perfusion than would be explained by only the structural damage (145). It has been postulated that focal damage may cause a disruption in the circuitry which then results in area of underuse or compensatory overuse in other parts of the circuit (154).

Brain insults that result from strokes or tumors are more likely than traumatic insults to involve a single area which makes localization somewhat less complex. Brain tumors located in the basal ganglia (162–164) and frontal lobes (165) have been reported to cause secondary OCD. Ischemic or hemorrhagic lesions to either the right or the left basal ganglia have been shown to cause OCD (147, 157, 166–168), although others have reported that bilateral damage is needed to cause these symptoms. In one case, a patient developed transient apathy after suffering an ischemic stroke to one side of the caudate. Two months later he suffered a second ischemic stroke to the contralateral caudate which then resulted in OCD symptoms (169). Strokes affecting the parietal lobe (170) and the frontal lobe (145, 156, 171) have also been reported to precipitate OCD. Following brain injury, the onset of OCD generally occurs shortly after the insult, although there are reported cases of a delayed onset of up to 7 months. In one report, new-onset OCD symptoms developed in four adults within 24 hours of a brain injury (152). The onset of the OCD may or may not be related to psychological reaction related to the trauma (149, 172). In these cases of delayed onset of OC symptoms, it is put forward that underlying structural damage done to the septohippocampal area from the brain injury then leaves the patient more susceptible to OCD in the face of ongoing psychological stressors (172). The nature of symptoms may change over time as well (159).

Similar to the case of TBI, the onset of OCD may begin abruptly after a stroke occurs. Depending on the location of the injury, there may or may not be associated neurological or cognitive sequelae that accompany the OCD. In the case of tumors, the onset would likely be more insidious. In one case, a 16-year-old male with a brain dysgerminoma affecting the left lenticular region and right internal capsule developed OCD symptoms, which then improved as the tumor was treated with chemotherapy. Changes in personality and the reappearance of OCD were one of the early signs indicating the relapse of the tumor on several separate occasions. With each episode, the symptoms improved as the tumor was treated (162). Similarly, acute hemiplegia and OCD developed in a boy secondary to a lesion in lentiform nuclei associated with a history of recent varicella infection. He was treated with sertraline and made a full recovery (173).

A wide variety of presentations have been reported in cases of secondary OCD many of which have the same constellation of symptoms as is seen in primary OCD (149, 157). One study comparing idiopathic OCD, acquired OCD and normal controls across a variety of neuropsychological indices, reported that similar deficits in attention, memory, language and executive functioning were seen in both OCD groups but not in the normal controls (157).

However, some cases differ in presentation. Although also seen in 20% of primary OCD, secondary OCD may be more likely to present with only obsessions or compulsions, rather than a combination of both (159, 174). Patients who showed significant apathy, lack of flexibility and treatment resistance in acquired cases of OCD were accompanied by a general lack of feelings of anxiety and depression (175). This lack of anxiety has been reported in those patients with damage primarily to the basal ganglia (147).

Few reports and no controlled studies exist in the treatment of acquired/secondary OCD. In some cases, treating the underlying disorder will successfully improve the OCD symptoms. For example, in one case a cranioplasty was instrumental in the resolution of symptoms in a patient following TBI, and in another case, chemotherapy successfully treated OCD caused by a dysgerminoma (176). Several cases report on the benefits that specific patients have derived from SSRIs including fluoxetine (145, 177). In one case, a patient with acquired OCD was successfully treated with fluoxetine 60 mg daily with a decrease in his Yale-Brown Obsessive Compulsive Scale (YBOCS) score from 30 to 10 over a 90-day period. In this case, there were multiple brain lesions shown on MRI including injuries to the orbitofrontal cortex bilaterally as well as low serotonin transporter density in the midbrain and hypothalamus shown on SPECT (178). Several authors have reported on the effectiveness of cognitive-behavioral therapy in addition to treatment with medications (161, 167). In one case, a 78-year-old male who developed OCD after an infarct to the left basal ganglia had minimal response to SSRIs but achieved significant improvement after undergoing cognitive behavioral therapy (CBT) in an intensive inpatient program. In this case, the patient's YBOCS went from 24 to 2 with good maintenance up to a year after treatment (167). Another group reported on the combination of cognitive rehabilitation and cognitive behavior therapy for a patient with a brain injury. In this case, memory problems after the injury lead to obsessional checking, and it was important to work on implementing an external memory system as well as engaging in exposure/response prevention in order to treat the OCD symptoms (179). In some cases, improvements using standard treatments for OCD are ineffective. In one case, a patient who developed OCD after a frontal lobe infarct failed to respond to more than 35 different medications (156). Despite the reports of treatment resistance, those patients with secondary OCD often will respond to traditional therapies.

Many challenges remain in systematically studying the onset of OCD after TBI and other brain injuries. Cases of acquired OCD are relatively rare, and often, rigorous evaluation is needed to tease out these symptoms. Eliciting symptoms of OCD may be difficult for inexperienced examiners, and symptoms of OCD that are elicited may be misattributed to other causes such as

Table 10.1. Medical aspects of OCD.

Brain structure	
	Stroke
	Tumor
	Parkinson's, other basal ganglia illnesses
	Head injury
	Morphology
Immune illness	
	Sydenham's chorea
	Multiple sclerosis
	SLE
	Acute disseminated encephalitis
	PANDAS/PANS
Neurochemical	
	Oxytocin, vasopressin
	Glutamate
	Serotonin
	GABA
	CRF
	Dopamine
	Medication-induced OCD
Psychological	
	Trauma
	Accommodation
Neuropsychological	
	Neurological soft signs
	Visual memory
	Executive function
Medical manifestations of OCD	
	Dermatologic
	Food restriction

decreased processing speed due to a neurological deficit versus obsessional slowness, or perseveration that is often seen in brain injuries vs. OCD. In addition, patients may be reticent to report OCD symptoms because of stigma or embarrassment. Further, symptoms often change significantly during the initial stages after an acute brain injury, which makes tracking psychiatric symptoms more challenging. Albeit uncommon, acquired OCD can provide insights into circuitry that has gone awry to produce OCD symptomatology (180). Please see Table 10.1.

10.9. Autoimmune Etiologies of OCD

Several autoimmune diseases have been shown to confer a greater risk of the co-development of OCD. Some cases of OCD may be related to various autoimmune diseases including systemic lupus erythematosis (SLE) (181, 182), multiple sclerosis (MS) (183–185) and acute disseminated encephalopathy (186). Another group reported a 10- to 15-fold increase in OCD in patients with SLE when compared to rates in community-based samples of OCD (181). Similarly, others have shown a higher than expected rate of OCD in patients with MS (185) and thyroid dysfunction (187, 188). On the other hand, evidence from a chart review (136) showed higher than expected rates of immune related disease in psychiatric patients with OCD when compared to patients with other psychiatric illnesses. The immune association that has been the most clearly shown is the association between some cases of childhood-onset OCD and group A streptococcal (GAS) infections (189, 190). Some symptoms in Sydenham's chorea (SC) overlap with those of primary OCD, including aggressive thoughts and contamination fears, and a higher than expected incidence of OCD is seen among patients with SC (191–194). Although it is not as striking, an increased incidence of OCD in rheumatic fever (RF) without chorea exists (195), occurring only during acute episodes of RF.

Over the past several years, significant strides have been made to characterize the association of OCD and tics with infectious triggers such as viruses (196), mycoplasma (197), Lyme disease (198), and GAS (199, 200). While tics and OCD that have a dramatic temporal association associated with GAS are termed PANDAS (201), a newer classification of acute and severe onset OCD does not require a specific infectious trigger, and is termed Pediatric Acute-onset Neuropsychiatric Syndrome (PANS) (202). In addition to OCD, these children often have dramatic changes in behavior and personality, mood disturbance, food refusal, frequent urination (pollakiuria), handwriting deterioration, sensory defensiveness, tics, hyperactivity, sleep disturbances, and separation anxiety (202). While the notion of an infectious trigger for OCD and tics has remained controversial, the concept

is not new. The first report of a potential association between infectious disease and tics occurred in 1929, when Selling reported on three cases of tics that were associated with sinusitis (203). Following that initial report, there have been many case reports, and more recently, case series further elucidating this phenomenon (199, 204–211). Some complications exist in attempting to investigate these cases. In many cases of infections, symptoms are subclinical and will therefore miss detection (212). In rheumatic fever, an illness which is clearly associated with GAS infections, one study reported that in upwards of 75% of cases, the onset of symptoms occurred with minimal or no evidence of a preceding case of pharyngitis (213). Further complicating the ability to establish a definitive GAS link to OCD symptoms is the observation that elevated GAS titers are common in the prepubertal age group (214), so a single elevated titer in a child with new-onset OCD would not imply a causal relationship with an infection nor does a specific titer value. Ideally, serial titers would be needed before, during, and after the onset of OCD symptoms to more convincingly correlate the infection with the onset of OCD/tic symptoms. Some children with tics and OCD, similar to reports in RF (215), may have persistent or an overactive immune response to GAS (216). This possible unique immune response may be a consequence of multiple factors including developmental and/or environmental influences. Titers may remain elevated for 6 months to a year without clear evidence of preceding streptococcal infection. For example, Murphy et al. found that those with a dramatically fluctuating neuropsychiatric symptom course had more evidence of persistent elevations in one or more strep titers compared to those that had a course inconsistent with PANDAS (217). This finding may be due to the relative proximity of the streptococcal infection at the time of study enrollment and then repeated streptococcal exposures without clinical pharyngitis leading to more severe and turbulent symptoms. Alternatively, a chronically activated immune system may be predisposed to other neuroimmunologic triggers such as stress and nonspecific infections (218, 219).

Frequent GAS infections may also predispose children to neuropsychiatric sequelae (220). Reasons for GAS recurrence are likely complex and numerous. Most of the recurrences are relapses, in other words, infection by the same streptococcal strain as opposed to new infections of a different strain (212). Reasons for relapse could include poor compliance or inadequate duration of antibiotic therapy, poor antibiotic penetration into lymphoid tissue, beta-lactamase producing bacteria inactivating the antibiotic's efficacy, alterations in protective microflora, re-exposure, or immunological defects (221). The consequences of recurrent tonsillopharyngitis are largely unknown. Many OCD/tic patients report onset of their neuropsychiatric symptoms after repeated streptococcal infections over the course of a few months (222). Published support for the risk associated with repeat GAS infections was a recent epidemiologic study that used population-based data from a large health maintenance organization (220) and found that patients with OCD or TS were more likely than controls to have had prior streptococcal infection in the 3 months before onset date. Having multiple GAS infections within a 12-month period was associated with a markedly increased risk for TS (OR = 13.6) (220). The number of prior GAS infections has been shown to correlate with a more severe course and a greater incidence of relapse (208). A school study examining motoric signs and behavior while obtaining monthly GAS cultures on 693 school children, found that those with repeated GAS infections during the 8-month study had more frequent neuropsychiatric findings (223). Further complications occur as some non-GAS strains may have a role in OCD symptoms. It has been shown that some virulent factors have transferred from GAS to group C and group G streptococcus (224), allowing these strains to activate the immune system without being detected by standard culturing techniques. Conversely, group C and G strep may cause false positive results, as these strains may lead to elevation in strep titers without causing a corresponding increase in OCD symptoms (217).

Seasonal variations are often seen in autoimmune illnesses (225). For example, the peak incidence of rheumatic fever is from January to March, which lags the peak incidence of GAS by a short period (226). In addition, rheumatic fever has lower rates in the summer months when GAS infections are also lower. Similarly, tic symptoms and acute exacerbations are seen at increasing rates in the fall and winter months which mirrors the increased rates of streptococcal pharyngitis during this time (217, 227). Other factors may be involved in this increased incidence, including increased upper respiratory tract infections caused by other viruses and bacteria during the fall and winter months and a general increase in stress levels because of school (196, 198). It is possible that some individuals have a heightened susceptibility to OCD/tics which are triggered by these other factors rather than GAS.

There are various theories as to how strep infections may cause OCD/tics. One of the best supported is the concept that antibodies produced against GAS proteins cross-react with host proteins that are similar in structure, a phenomenon known as molecular mimicry. Damage to the blood–brain barrier may allow these antibodies to pass into the central nervous system where they may act as agonists or antagonists to receptors in the basal ganglia or may cause an inflammatory response in these brain areas. In attempting to further characterize this process, drawing parallels with Sydenham's chorea is potentially helpful. In SC, there is a well-characterized rise in anti-basal ganglia antibodies to the caudate (228). Similarly, an increase in antibodies has been found to the caudate in patients with Tourette's syndrome (206, 229). Despite the presence of some positive studies, there are also several studies using different techniques and epitopes, which show minimal differences in antibody binding when comparing patients with OCD/tics to controls (230–233). It has been postulated that these negative results may be the consequence of benign autoimmunity (false positives) among the control group or tests that lack the level of sensitivity needed to detect these changes (230–233). The symptoms of PANDAS and SC may be mediated by direct effects of cross-reactive antibodies on receptors in the basal ganglia affecting signal transduction and subsequent release of excitatory neurotransmitters (229, 234, 235).

While PANDAS is, by definition, seen only in the pediatric population, immunological abnormalities that are present in adult cases of OCD have been evaluated by peripheral cytokine profiles, lymphocyte subsets, viral antibodies, and autoantibodies (236–239). Some have shown abnormalities in immune function in adults with OCD (237, 240), although other studies do not (236, 241, 242). The need for further investigation is emphasized by the mixed results of adult OCD immune function studies, small sample size and lack of evidence to determine the relative contribution of alterations in the HPA axis due to stress versus autoimmunity. Other evidence of immune alterations seen in OCD and/or tic disorders reflects changes in indices for cellular, cytokine, or markers of inflammation (200, 219, 243–249).

10.10. Medication-Induced Obsessive Compulsive Symptoms

Certain pharmacologic agents, such as methylphenidate/dextroamphetamine (250), zonisamide (251), and m-chlorophenylpiperazine (m-CPP) (252) have been reported to trigger obsessive compulsive symptoms (OCS). In addition, worsening or production *de novo* of OCS related to the use of atypical antipsychotics has been documented in numerous case reports, despite their anti-obsessional effects in OCD (253). In terms of frequency, most cases involved the use of clozapine, followed by risperidone, olanzapine, and quetiapine. Clothiapine, an antipsychotic related to clozapine, has also been reported to cause OCS (254). There has been no case report of OCS related to the use of aripiprazole or ziprasidone yet. Interestingly, all antipsychotic-induced OCS have involved patients with primary psychotic disorders, mostly chronic schizophrenia, rather than pure OCD (253). In most cases, OCS emerged 3–15 months after the medication was started and was of transient nature (253). Co-administration of a selective serotonin reuptake inhibitor (SSRI) diminished OCS in some patients receiving clozapine (255). Given the higher affinity for serotonin 5-HT_2 receptors than dopamine D_2 receptors at low dose, 5-HT_2-receptor antagonism has been postulated to play a role in atypical antipsychotic-related OCS, whereas anti-obsessional effects may occur through D_2 receptor antagonism at higher dose (253, 256). In concordance with this hypothesis, Ramasubbu et al. reported reversal of risperidone-induced OCS by increasing the doses of risperidone in a patient with bipolar disorder and comorbid OCD (256).

In summary, all cases of atypical antipsychotic-induced OCS involved patients with primary psychotic disorders, rather than pure OCD. This phenomenon further suggests that the interplay of serotonin and dopamine may be substantially different in pure OCD versus primary psychotic disorder with comorbid OCD (257). In addition, the anti-obsessional effect of atypical antipsychotics may be more pronounced at higher does (256, 257).

10.11. Medical Consequences of OCD

It is well known that OCD can be very debilitating, limiting patient's ability to work, maintain meaningful relationships and affect multiple areas of quality of life. What has been less well documented are some of the potential medical consequences of OCD (258–260). The most clearly documented medical consequences of OCD involve dermatological problems. Several studies have been done examining the rates of patients with OCD who present in outpatient dermatology clinics. One study looked at 92 consecutive new evaluations to a dermatology clinic and found that 18 patients (20%) met criteria for OCD, only one of whom had a prior diagnosis of OCD. In this study they showed that the dermatologic diagnoses varied widely and were not necessarily directly related to OCD (261). Another study, focusing on pruritic dermatological conditions found 14% of a randomly selected group of patients had OCD, which had not been previously diagnosed (262). Further supporting the high rates of OCD among dermatologic patients, another study looked at 166 patients for OCD and found that 41 patients (24.7%) met criteria for OCD; only six had been previously diagnosed. In this study, the most frequently seen obsessions were contamination fears (61%), pathological doubting (53.7%) and need for symmetry (51.2%), and the most common compulsions were excessive washing (61%), checking (51.2%) and orderliness (41.5%). Of the various dermatological diagnoses such as sebaceous gland diseases (eg., rosacea, acne) eczema, pruritis, urticaria, and psoriasis, there were no statistical differences between the OCD and non-OCD groups in the frequency of dermatological illnesses except sebaceous gland diseases which appears unrelated to most OCD symptoms except the potential of being exacerbated by stress (263). Perhaps this finding has more to do with proposed immune dysfunction in patients with OCD. Although in psychiatry clinics, patients with OCD often have dermatitis from excessive hand-washing or the use of chemical cleansers, in a dermatology clinic, the increased incidence of OCD appears to be unrelated to specific OCD symptoms or anxiety. Perhaps patients with dermatological sequelae from OCD related disorders such as excessive skin picking, lip licking, trichotillomania, and nail biting, do not frequently seek dermatological consultation.

Other potential medical consequences that may be due to OCD include those related to food refusal and decreased motor movements. There have been cases where patients have refused to eat and lost enough weight that placement of a gastric feeding tube has been necessary. Some obsessions that may lead to this type of food refusal include fear of eating poisoned or contaminated food. In one case, a patient refused to eat after developing an obsessive fear that he had swallowed a utensil (264).

In addition to the obvious complications of weight loss, the need for placement of a gastric tube confers the added risk of bleeding or infections and clearly places patients at significant medical risk. Decreased motor movements, and catatonia, are also potentially severe results of OCD with diminished use of muscles, with subsequent potential for muscle atrophy over time. Although very rare, cases with prolonged catatonic states that were part of severe OCD and responded to conventional OCD treatments have been described (265, 266). Patients who refuse to get out of bed may develop bedsores and orthostasis and general weakness over time. While these are clearly rare and exceptional risks of OCD, they have been noted and are worthy of consideration. In addition, cases of pica have been reported to be secondary to OCD (267).

10.12. Treatment

10.12.1. Behavioral

Exposure-based CBT for OCD is a skill-based treatment approach which has been found to be efficacious in clinical trials and has shown excellent maintenance of symptom reduction at follow-up (268–272). The premise that compulsions are performed to reduce or avoid anxiety that is associated with obsessions underlies CBT for OCD. CBT is composed of three core components: exposure, response prevention, and cognitive restructuring. *Exposure* relies on the gradual decrease in anxiety after being exposed to a feared or ritual-provoking stimulus. This leads to decreased elevations in anxiety and more rapid attenuation of distress in future exposures. *Response prevention* is based on the assumption that rituals and compulsions serve to reduce anxiety in the short-term through negative reinforcement, escaping and/or avoiding distress. Individuals with OCD perform rituals to relieve anxiety, and never have the experience of natural anxiety reduction. Response prevention exercises allow for the anxiety to naturally subside by requiring the patient to avoid performing their compulsion so the anxiety can be reduced through habituation. Variations of CBT with response prevention include weekly CBT, intensive CBT, family-based CBT, group CBT, individual CBT, and web-based CBT (268, 271–273).

10.12.2. Pharmacological Treatment

While CBT is clearly an effective treatment for OCD, there is evidence that the combination of psychotherapy and pharmacotherapy achieves greater response rates in some patients than either modality alone (269, 273, 274). Pharmacological treatment should be considered to be more of a first-line option if there is significant impairment in functioning, past therapy has shown little improvement, comorbid conditions will interfere with therapy or if the patient is psychotic.

Serotonin (5-hydroxytryptamine, 5-HT) has remained the leading target for investigations of the neurochemical underpinnings of OCD, largely because of the remarkable efficacy of SSRIs in the treatment of OCD. While the role of the 5-HT system appears to be more important in the treatment than in the etiopathology of OCD, more direct measures of neurochemical dysfunction, including paradigms that employ biological markers, pharmacologic challenges, or functional neuroimaging are needed to corroborate the pathophysiologic role for 5-HT.

Acute blockade of 5-HT reuptake appears to be the critical first step in a chain of neural events leading to efficacy in the treatment of OCD. It is believed that long-term SSRI treatment likely produces its effects by enhancing 5-HT concentrations in the synaptic cleft which, after prolonged exposure, ultimately leads to desensitization of presynaptic 5-HT1B autoreceptors in various brain regions (275). This desensitization occurs with varying time courses in different regions of the brain. Structures that are involved in depression, including the hippocampus and hypothalamus have been shown in animal models to achieve desensitization within 2 weeks (276). In contrast, the prefrontal cortex (PFC), thought to be the main target in the treatment of OCD, does not undergo desensitization for up to 8 weeks (276). In addition, animal studies have indicated that higher concentrations of SSRIs are needed to achieve desensitization in the PFC than in the hypothalamus and hippocampus (277). These observations are congruent with clinical experience that longer medication trials and higher doses of medications are needed to achieve therapeutic benefit in the treatment of OCD than those needed in the treatment of depression.

Many studies have demonstrated the efficacy of SSRIs in the treatment of OCD in both adults and children (278). The clear superiority of this class of medications makes them the first-line treatment for OCD. Clomipramine (CMI), a tricyclic antidepressant with fair specificity for serotonin reuptake, was the first medication to show clear efficacy for the treatment of OCD (279). In adults, response rates for SSRIs and clomipramine have been reported to be between 40 and 60% of participants, compared to less than 20% for placebo (280). CMI and SSRIs consistently show superiority over placebo in the treatment of OCD symptoms (281–289). In meta-analyses of CMI compared to other SSRIs, CMI continues to show better efficacy than any single SSRI or SSRIs as a pooled group in both children and adults (280, 290, 291), although this superiority has not been shown in individual trials comparing CMI directly to fluvoxamine, paroxetine or fluoxetine (280). No clear differences in efficacy have been shown when comparing any single SSRI to another, and it is generally accepted that except for possibly CMI; all SSRIs are essentially equally effective.

Despite CMI's superiority in these studies, it has significant liabilities including a more significant side effect profile, the need for cardiac and plasma monitoring, and the increased risk of serious adverse events including cardiac arrest and death. For these reasons, although CMI may be considered the *"Gold Standard"* treatment of OCD, it is not generally felt to be a first-line agent. Instead, SSRIs are considered to be first-line medications in this disorder (292). Given the relative similarity among the SSRIs, the choice should be based on medical history, concomitant medications, and the adverse effect profile. Factors to consider include half-life, active metabolites, linear vs. nonlinear metabolism, CYP-450 inhibition, and side effects. Some side effects of the SSRIs include nervousness, insomnia, restlessness, nausea, and diarrhea. Concerns regarding increased suicidality in patients taking SSRIs prompted the FDA to require "black box" warnings on all SSRIs to increase physician awareness and knowledge of this issue, although there is a great deal of controversy regarding both the new requirements and the findings (293).

Once a medication choice has been made, it is important to address several important issues in the treatment of OCD. First, 10–12 weeks at adequate dosage is necessary to evaluate the efficacy of the medication (287). It is generally accepted that if one SSRI fails, a second SSRI should be tried, as failure of one does not mean that all SSRIs will be ineffective. If, however, symptoms remain unresponsive to trials of multiple SSRIs, augmentation may be necessary (287, 294). Although there are few studies looking at continuation of medication following improvement of symptoms, it is thought that ongoing administration of the medication at the treatment dose will be necessary for at least 1–2 years following the improvement in symptoms prior to tapering and discontinuing the medication to minimize risk of relapse. However, some patients need to be maintained on their medication for several years (287).

Many augmentation strategies have been attempted in the treatment of OCD (295). Given the benefits of enhancing the serotonin system in the treatment of OCD, one such strategy was aimed at increasing serotonin via other mechanisms. However, studies examining SSRI administration with the addition of lithium (296–298), buspirone (299–301), and clonazepam (302) have shown little effect. A second strategy is based on the observation that repetitive stereotypies and OCD-like behaviors can be produced in humans by the administration of exogenous D2 agonists or stimulants. This observation, along with the well-known comorbidity of tic disorders and OCD have led to the theory that excess dopamine may be involved in the pathophysiology of OCD. Subsequently, the most promising augmentation strategy to date has been the addition of antipsychotic medications to SSRIs. Several studies examining SSRI augmentation with the low dose dopamine antagonists pimozide (303) and haloperidol (304, 305) showed clear benefits in the treatment of OCD symptoms, particularly in patients who had comorbid tics or schizotypal personality disorder. Further studies looking at augmentation with low dose risperidone have shown similar improvements in treatment refractory OCD (305–309), although differences were not seen in the benefits for patients with comorbid tics or schizotypal personality disorder when compared to patients without these comorbidities. Studies have shown mixed results with augmentation of quetiapine, with some studies showing benefit (310, 311), while others showed no statistically significant improvements over placebo (312, 313). Augmentation with olanzapine has also shown mixed results. One study, which added olanzapine after an 8-week trial of fluoxetine showed no increased benefit over extension of the SSRI-only treatment group (314), while a second study, showed significant improvement in OCD symptoms after the addition of olanzapine (315). Given the number of reports of OCD improvement with aripiprazole, a partial dopaminergic agonist and partial 5-HT1A agonist, it is perhaps one of the more promising augmentation strategies (316–320). It has a milder side effect profile than most typical or atypical antipsychotics, particularly regarding sedation, extrapyramidal symptoms, cardiovascular effects, or elevations in serum prolactin.

Dysfunction of glutamatergic neurotransmission has been implicated in the pathophysiology of OCD (321) and recent clinical reports suggest that some glutamate modulating agents are efficacious in the treatment of this disorder (322, 323). Rosenberg and colleagues (2000) have shown an elevation of a glutamate signal in the caudate of children with OCD using ^{1}H nuclear magnetic spectroscopy (77). Furthermore, this elevated signal normalized following effective SSRI treatment. The precise mechanism of SSRI modulation on the glutamate signal is not known. Other agents may exert such a dampening effect on glutamate release such as riluzole (324) and *N*-acetylcysteine (325). Memantine, a non-competitive NMDA receptor antagonist has shown promise as an augmentation strategy in OCD (80, 326). In addition, direct antagonists of the postsynaptic AMPA-type glutamate receptors such as topiramate that moderate the excitatory action of this neurotransmitter in the head of the caudate nucleus could have anti-OCD activity (327, 328). NMDA partial agonist D-cycloserine (DCS) has been proposed to facilitate cognitive behavioral therapy of anxiety disorders; small studies thus far have had positive outcomes (329) and negative outcomes (330). The use of DCS with CBT in the treatment of OCD has recently been studied (331, 332). It is proposed that DCS decreases the time needed to reach therapeutic targets (333, 334). Other agents with the potential to affect the glutamatergic system include beta lactam antibiotics (335), which may add an interesting dual action in children with PANDAS/PANS (336). Any agents affecting this system would have to be fairly selective for such neurons to avoid generalized adverse events due to generalized attenuation of glutamate transmission.

In many patients when OCD is comorbid with tics, bipolar disorder, or schizophrenia, combination of medications is frequently required. Comorbidity often clearly effects a negative treatment response (337) as demonstrated in one pediatric trial (338). Those with "pure" OCD had a much higher response rate than those with comorbid disruptive behavior disorder. The impact of comorbidity on treatment response needs further research and exploration.

10.12.3. Neurosurgical and Brain Stimulation Approaches to Treatment

The ability to perform minimally invasive psychosurgery for very severe and chronic neuropsychiatric disorders has made tremendous gains in the last few years. Ablative techniques such as cingulotomy, anterior capsulotomy, limbic leucotomy, and gamma knife capsulotomy have been used for very refractory cases of OCD with some success but at the risk of irreversible effects such as personality changes and residual neuropsychological deficits (339). Brain stimulation techniques such as deep brain stimulation (DBS), electroconvulsive therapy (ECT), vagus nerve stimulation (VNS), and repetitive transcranial magnetic stimulation (rTMS) have all been tried with varying success in treatment refractory OCD (340). DBS is currently being performed in refractory OCD cases (341, 342). DBS has the added benefit of very specific targeting of the regions likely involved in the neurocircuitry mediating OCD symptoms (such as anterior limb of the internal capsule) and the reversibility of the procedure (removal of stimulator, clipping leads) (343).

10.12.4. Treatment Relevant to PANDAS

The current standard of care for PANDAS/PANS is the same as that for OCD and tic disorders; namely, treat with SSRI and/or CBT and follow the course of illness. While immune-based treatments are being researched (i.e., antibiotics, intravenous immunoglobulin, plasma exchange), it is reasonable to check for an active infection (GAS rapid test or culture, influenza rapid test, etc.) for a child presenting with an acute and severe onset presentation of OCD. In order to mitigate high risk therapies in patients that are not clearly PANDAS/PANS and to assist clinicians with a suspected case of PANS/PANDAS, clinical guidelines for assessment and treatment are under development.

10.13. Conclusions

OCD is a fascinating disorder from a neurobiological point of view because the repetitive behaviors and thoughts associated with OCD have an array of rather unique characteristics: 1) they echo phylogenetically old behaviors (e.g., nest building, grooming) that are programmed into vertebrate brains, 2) they can result from genetic predisposition as well as acquired brain lesions that affect frontal-subcortical circuits, 3) they are triggered and exacerbated by anxiety and stress, 4) they can result from dysregulation of multiple neurotransmitters (dopaminergic, glutamatergic, and serotonergic systems), 5) they may be triggered as an inflammatory or immune mediated response to infections, 6) they increase with repetition (e.g., reward or practice, a characteristic "striatal" pattern) and are decreased by exposure and response prevention in controlled therapeutic settings. Given what we know about frontal-striatal circuitry, it would appear that OCD is not the result of a single specific factor, such as too little serotonin, too much dopamine, too much anxiety, but rather reflects dysregulation or imbalance of the striatal system. This system serves to integrate "hard-wired" motor and cognitive programs with newly learned programs. Thus, if the system becomes dysfunctional, one would expect to see impaired selection and "sticky" shifting of motor and cognitive behaviors.

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11
Somatizing and Dissociative Disorders

C. Robert Cloninger, M.D., Ph.D. and Mehmet Dokucu, M.D., Ph.D.

Abstract Most patients consulting physicians have a mixture of physical and mental complaints that require careful differential diagnosis. Somatization is the production of recurrent and multiple physical symptoms in excess of any underlying medical disorder. Patients may have well-documented medical diagnoses, but their complaints are excessive or disproportionate in the judgment of the clinician. In DSM-5 the diagnosis of somatization emphasizes the presence of characteristic positive symptoms and signs for the diagnosis, whereas in DSM-IV the emphasis was on the absence of a medical explanation. DSM-5 makes it clear that the clinician is making a judgment about the complaints being excessive rather than on the absence of any medical diagnosis, but with either criterion, the clinician must make a judgment about the underlying medical basis for the complaints. The assessment and treatment of somatizing disorders requires patience and compassion to maintain a therapeutic alliance, and randomized controlled trials show that treatment with antidepressants, cognitive-behavioral therapy, or mindfulness-based therapies reduce health care utilization and subjective distress.

Somatization Disorder is the best-validated prototype of somatizing disorders, so we will use the adjective "somatizing" to specify the group of disorders referred to as "somatoform disorders" in DSM-IV and as "somatic symptom disorders" in DSM-5. Somatization Disorder has been shown to be a chronic and heritable disorder that is clinically manifest with complaints of multiple bodily pains, gastrointestinal, psueudoneurologic symptoms, sexual, and reproductive symptoms. Unfortunately, general medical practitioners found the criteria for Somatization Disorder in DSM-IV to be time-consuming to apply, so for their convenience DSM-5 has introduced an easy-to-use category of Somatic Symptom Disorder that may be diagnosed on the basis of a single somatic complaint that the clinician judges to be excessive, even though much research shows that such subjective judgments are unreliable. Conversion disorders involve acute or chronic loss of voluntary sensorimotor functions, such as psychogenic blindness, paralysis, or tremors, that can be shown to be inconsistent with neuroanatomy and neurophysiology. In DSM-5, conversion disorders may be diagnosed in the absence of a known psychosocial stressor because recent research has shown that the inconsistent neurological signs are a more reliable basis for the diagnosis. In contrast, some somatizing disorders more closely resemble physical phobias (e.g. hypochondriasis) or social phobias (e.g., body dysmorphic disorder).

Dissociative disorders involve the disruption or loss of the integrative mechanisms of consciousness, memory, identity, or perception. Dissociative disorders include amnesia (a disruption of memory), fugue (a disruption of identity), depersonalization (a disruption of perception), and Dissociative Identity Disorder (a disruption of consciousness and identity formerly called Multiple Personality Disorder). In dissociative disorders, transitions between personalities or the onset of amnesic or fugue states are usually precipitated by psychosocial stress like those observed in conversion disorders. Thus both conversion and dissociative disorders are typically precipitated by severe psychosocial stress, but it is often difficult to elicit the relevant history before treatment until the clinician can contact collateral informants. Recent brain imaging results suggest that hyperactivity of the anterior cingulate cortex can actively inhibit motor activity (e.g. psychogenic paralysis), sensory perception (e.g., psychogenic anesthesia), memory (e.g., amnesia), or identity (e.g. fugue) as a defensive response to stressors.

C.R. Cloninger, M.D., Ph.D. (✉)
Wallace Renard Professor of Psychiatry, Washington University School of Medicine, St. Louis, MO, USA
e-mail: clon@tci.wustl.edu

M. Dokucu, M.D., Ph.D.
Assistant Professor, Department of Psychiatry and Behavioral Sciences, Northwestern University
Feinberg School of Medicine, Chicago, IL, USA
e-mail: m-dokucu@northwestern.edu

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11.1. Introduction: The Dualism of Psychogenic Versus Physiological Is False

Most physicians are tempted to try to separate patients who have a mixture of physical and psychological complaints into those who have psychogenic versus physiological complaints. The temptation has always been strong because of the common belief in mind–body dualism. Unfortunately, such dualistic thinking cannot capture the complex interactions among the components of a human being, so physicians have long been frustrated in their efforts to understand psychosomatic disease processes. For example, patients with well-documented epilepsy often have some conversion reactions ("pseudoseizures") (1, 2). Patients with non-physiological findings that change with sedation or suggestion are often later documented to have medical disorders with well-defined organic causes.

Yet psychiatrists and other physicians persist in subscribing to the dualistic idea that signs and symptoms of illness are either psychologically initiated under voluntary control or they are the result of involuntary pathophysiological mechanisms. Such simplistic thinking is elaborated and enshrined in the Diagnostic and Statistical Manual (DSM) for mental disorders, as shown in Table 11.1. Somatoform and dissociative disorders are presumed to be associated with psychological factors and not fully explained by any physical mechanism, such as a medical condition associated with many somatic complaints like hyperparathyroidism (3). In addition, they are not intentionally produced (as in "factitious disorders") or feigned (as in "malingering"). These distinctions are conceptually clear in the abstract, but lead to many problems in practice because they are based on a false dualistic concept of human nature.

First of all, the distinction between psychological and physical disorders is not reliable in the vast majority of cases of somatizing disorders. The most common somatizing disorder in primary care was called "undifferentiated somatoform disorder" in DSM-IV and required only one symptom that is not fully explained by a known general medical condition to the satisfaction of the examining physician. Unfortunately, many physicians assume that a symptom is psychogenic in origin if the patient appears too anxious, too dramatic, too indifferent, or responds to suggestion, sedation, or obtains secondary gain from their complaints (1). However, many people with well-documented physical disorders have many of these features, as summarized in Table 11.2. Many people get anxious or take advantage of their symptoms when they get sick, and may show non-specific and transient improvement when they are relaxed (4). Past history of somatizing disorders predict more of the same, but what are often assumed to be current features of psychogenicity are an unreliable basis for understanding the etiology and prognosis of the complaints (5–7). Personality disorders also vary widely in their association with somatizing disorders as seen in Table 11.2. Some character disorders are associated with a high risk of somatizing disorders (e.g., borderline and antisocial personality disorders), but others are associated with a low risk. This suggests that there may be different routes to disorders of character that depend on individual differences in the intelligence of different aspects of our being (i.e., the body, the thoughts, and the soul).

Second, the classification encourages psychiatrists to think in terms of whether someone has a mental or a physical disorder, when these are often comorbid. Chronic lifestyle choices and patterns of stress reactivity lead to many chronic medical conditions. Most complaints to primary care physicians are associated with psychosocial stress. Primary care physicians prescribe more psychotropic drugs than do psychiatrists. Effective care of general medical conditions requires good mental health care, and vice versa. The realms of physical disease and mental disease are not really separable.

Third, the classification encourages psychiatrists to think like a detective, judge, or adversary, rather than a hopeful, compassionate, encouraging, and truth-seeking caregiver, about whether someone is faking or not. In fact, people with factitious disorders or malingering often have severe mental disorders that require treatment, though not treatment for the complaint that they are making. Even if a patient is judged to have a somatizing disorder, they are often left to feel that the doctor thinks the problem is not real because the doctor implicitly communicates that what is real is in the body (8). Exclusion of general medical conditions seems to imply to many that the problem is imagined, dramatized, or exaggerated "in excess of what is expected" in

TABLE 11.1. DSM-5 criteria used in the differential diagnosis of symptom(s) suggesting physical illness.

Classification	Physical mechanism explains the symptoms	Symptoms are linked to psychological factors	Symptom initiation is under voluntary control	Obvious recognizable environmental goal
Somatic symptom and dissociative disorders	No	Yes	No	Variable
Factitious disorders	Variable	Yes	Yes	No
Malingering	Variable	Variable	Yes	Yes
Psychological factors affecting medical condition	Yes	Yes	No	Variable
Undiagnosed general medical condition	Variable	Variable	No	No

TABLE 11.2. Utility of psychiatric criteria for distinguishing conversion and dissociative reactions from physical disorders.

Putative diagnostic criteria	Predicts no physical disorder
Past history	
Somatization Disorder	Yes
Prior history of conversions	Yes
Prior history of somatic complaints	Yes
Personality disorder	
With prior history of somatic complaints	Yes
No prior history of somatic complaints	No
Current presentation	
Excessive worry or La belle indifference	No
Current anxiety or dysphoria	No
Excessive time and energy devoted to health concerns	No
Emotional stress before onset	No
Secondary gain	No
Partial improvement with suggestion or sedation	No

their medical condition (to quote DSM-IV). DSM-5 continues this emphasis on "excessive thoughts, feelings, or behaviors related to somatic symptoms or associated health concerns,"—even though the body makes contributions to thought and vice versa. For example, people who are high in Harm Avoidance are prone to anxiety and have more intense pain responses given the same objective stimulus than do people who are lower in Harm Avoidance. Their increased pain sensitivity is real, although it may *appear* exaggerated to someone who does not appreciate their unique pattern of reactivity, because the release of endogenous opioids is objectively reduced in anxiety-prone individuals (9, 10). Personality traits like Harm Avoidance predispose to anxiety, which in turn amplifies somatosensory perception and intensifies the experience of pain (11). The dualistic concept underlying the DSM classification of somatizing disorders may put the physician in a judgmental position that makes it difficult to establish a cooperative and respectful therapeutic alliance. The contributions of the soma (i.e., the body), the psyche (i.e., the soul), and the thoughts and memories with which they communicate, all make real contributions to current symptoms.

Fourth, the classification fails to recognize the inseparability of the body, the thoughts, and the spirit of every person as an integrated whole. Each aspect of our being has its own form of intelligence, and our healthy functioning requires that our multiple forms of intelligence be integrated. The intelligence of the body is displayed by a ballet dancer or an acrobat; the intelligence of analytical thought is displayed by an intellectual or logician; the intelligence of the soul is displayed by a wise contemplative mystic. The emotional intelligence of a person is a characteristic of the limbic system of his/her brain, which influences nearly every system of the body through the hypothalamic-pituitary-adrenal axis. The limbic system interacts constantly with higher cortical systems that underlie rational thought. The cognitive and emotional life of a human being is a complex and dynamic process that depends on the inseparable interplay of the body, the thoughts, and the soul of the person as a whole (12).

Despite all these problems with DSM, the syndromes described within it can be used effectively in patient assessment and treatment if a coherent concept of human nature is recognized and the classification is not reified into a description of discrete disease entities. In particular, in order to understand somatizing and dissociative disorders, it is crucial to have a broad understanding of both the cognitive components of the human body and the somatic components of human thought. In other words, it is important for a psychiatrist to understand that there are marked differences between people in the degree to which they are self-aware of the functions of their body and its sensations, drives, emotions, intelligence, and sentiments. An understanding of the degree of self-awareness of the body is particularly useful for the treatment of chronic somatizing and dissociative disorders like Somatization Disorder or Multiple Personality Disorder. It is also important for a psychiatrist to know how to appease and calm the emotional brain of an individual so that the short-circuiting of the rational parts of the brain can be stopped in order to treat acute somatizing and dissociative disorders like conversion reactions or fugue states. Psychiatrists often become accustomed to treating patients with medications or with talk therapy, but these methods are simply inadequate with patients with somatizing or dissociative patients. Somatizing and dissociative patients are people whose chief problems are difficulties in understanding and coping with the signs and symptoms of their own body. Accordingly, they need therapies that address the needs of their body in the language of the body, which requires experiential methods that are concrete and tangible.

11.2. Emotional Drives and Emotional Intelligence

People differ markedly from one another in their emotional style. Nearly 2000 years ago, Galen recognized four temperaments that he attributed to the effects of different body humors: the melancholic (due to melancholy or black bile), the choleric (due to choler or yellow bile), the sanguine (due to blood), and the phlegmatic (due to phlegm). The four humors were body fluids con-

TABLE 11.3. Descriptors of individuals who score high and low on the four temperament dimensions as measured by the Temperament and Character Inventory (reproduced with permission of the author; for more detailed descriptions, see http://psychobiology.wustl.edu).

	Descriptors of extreme variants	
Temperament dimension	High	Low
Harm Avoidance	Shy	Outgoing
	Pessimistic	Optimistic
	Fearful	Daring
	Fatigable	Vigorous
Novelty Seeking	Exploratory	Reserved
	Impulsive	Rigid
	Extravagant	Frugal
	Irritable	Stoical
Reward Dependence	Sentimental	Critical
	Sociable	Aloof
	Warm	Detached
	Sympathetic	Independent
Persistence	Perfectionist	Pragmatist
	Industrious	Apathetic
	Determined	Spoiled
	Ambitious	Underachiever

sidered responsible for a person's health and emotional disposition. People were thought to have a predominance of one of these, which determined their emotional body type. Modern personality research confirms the presence of four temperaments but has shown that these vary quantitatively. Descriptions of people who score high or low on each of these four personality traits are given in Table 11.3. These personality traits are approximately normally distributed with about one-third of people being near average and the two extremes being designated as high or low scorers (13). These traits are all about equally influenced by individual differences in genetic factors and in variables unique to each individual (such as spiritual or environmental influences that are not familial). These traits are called temperaments because they involve differences in the regulation of basic body emotions and aspects of social relationships that are regulated by the oldest part of the human brain, the limbic system: fear (driven by Harm Avoidance), anger (driven by Novelty Seeking), disgust (driven by Reward Dependence), and ambition (driven by Persistence).

Rather than there being only four types of emotional predisposition, everyone has some score on all four dimensions. All possible combinations of profiles on these four temperaments are observed in the general population, thereby maintaining extensive variability in the population. The variation is maintained because there are both advantages and disadvantages to the extremes of each temperament. For example, consider the extremes of Harm Avoidance. If a person is too shy and pessimistic, she/he will miss many opportunities that could have benefits but at the same time she/he is less likely to be exploited or to be killed in dangerous circumstances. On the other hand, a person who is too optimistic, will not experience much anxiety, but may get killed from his or her risk-taking. For the extremes of Novelty Seeking, a person who is highly impulsive will explore opportunities quickly but also may get into frequent fights because of his or her quick temper; a person who is highly rigid will be orderly and conserve resources well, but has difficulty making inquiries and asserting him- or herself. For the extremes of Reward Dependence, a person who depends on external approval may make many friends but she/he is also vulnerable to peer pressure and exploitation, whereas a person who is cold and aloof will be independent-minded but isolated without much social support or help in times of need.

Temperament is the emotional core of human personality and it has substantial influences on our pattern of human relationships. Our relationships with people are often formed quickly and outside of our consciousness because emotional reactions among people have evolved to be quick and partly unconscious in the ancient limbic system of the human brain that is shared with reptiles and mammals that evolved millions of years ago (14). People have the capacity to become self-aware of their emotional reactions and feelings of relationship to one another by means of limbic cortical communication via the Papez circuit that connects the anterior cingulate cortex with the hypothalamus, thalamus, and hippocampus (15). The anterior cingulate cortex provides a key interface for the regulation of emotional drives, cognition, and motor behavior (16). As a result, it plays a key role in contemporary neural models for the heterogeneous category of major depressive disorder (17). The size of the anterior cingulate cortex and its functional connectivity with cortical and limbic structures is strongly moderated by temperament traits, particularly Harm Avoidance (18–20). Accordingly, emotional stress from sexual, physical, and mental trauma can precipitate overactive emotional responses at the expense of higher cortical processes, thereby short-circuiting or hijacking the function of the rational and self-aware parts of the brain. In particular, somatizing and dissociative disorders are associated with overactivity of the anterior cingulate cortex and highly variable over- or underactivity of various parts of prefrontal cortex (1, 21).

The degree to which a person has self-awareness of their body and the responses regulated by its temperaments may be defined as his or her "emotional intelligence" quotient (EQ). This definition is more specific than definitions that equate emotional intelligence to character in general (22, 23). Emotional intelligence can be dissociated from the speed and accuracy of information processing in rational thought, which depends largely on working memory capacity and is measured by capacity for intellectual analysis or IQ. Both EQ and IQ can also be dissociated from wisdom or spiritual intelligence quotient (SQ) (24–26). People can be high in EQ and/or IQ, but not wise in a spiritual sense. Wisdom leads to a combination of foresight, creativity, well-being, and virtuous living, so wisdom supercedes EQ and IQ in scope. Wisdom provides a holistic intuitive awareness of the whole being that allows it to integrate reason and love in action.

When a person is wise, emotional and intellectual intelligence are integrated in action and augmented by well-being and virtues. There is also the emergence of self-transcendent character traits associated with self-awareness of certain subtle sentiments like awe, humility, self-abnegation, reverence, and compassion, described in more detail later. These self-transcendent sentiments and the self-transcendent values that arise from the experience of these sentiments provide a phenomenological basis for describing the spirit of a person.

In summary, there are three dissociable forms of intelligence that a clinician can recognize in every human being: emotional intelligence of the body, analytical intelligence of rational thought, and spiritual intelligence from listening to the soul. Emotional intelligence and spiritual intelligence are both important for character development, and deficits in either or both can lead to personality disorders. On the other hand, IQ has little impact on the risk of personality disorder, but it can contribute to personal and social complications from personality disorders. When emotional intelligence is deficient, then the risk of somatizing and dissociative disorders is increased. Therefore, to understand the etiology and treatment of somatizing and dissociative disorders, we need a fuller description of deficits in emotional intelligence.

11.3. Alexithymia: Deficits in Emotional Intelligence

Alexithymia is a deficit in the self-awareness of emotions that results in difficulties in the regulation of emotions and particularly a reduced emotional and fantasy life and difficulty in identifying, understanding, and describing the emotion of one's self and other people (27, 28). The term was coined from the Greek for "lack of" (*a-*), "words" (*lexis*), and "emotions" (*thymos*), so it literally means "lack of words for emotions". However, the literal meaning is misleading because the designated patients can describe their emotions with words, although not with much depth of understanding. In other words, they lack insight into the causes, significance, and regulation of emotions. Essentially alexithymia refers to a deficit in intelligence about the understanding and regulation of emotions.

The syndrome was first described when Peter Sifneos and John Nemiah observed that many of their patients with somatizing disorders had so much difficulty talking about their emotions that they did not respond well to insight-oriented psychotherapy. These patients also usually had other common features, including a stiff posture, an externally oriented focus on concrete functional details, and a barren fantasy and dream life with little emotional content (29). Subsequently extensive research has shown that alexithymia can be reliably measured, is distinct from other measures of personality, and is associated with increased risk of somatizing and dissociative disorders more than other mental or physical disorders (28, 30–34).

A fuller description of the deficits in emotional intelligence in people with alexithymia is presented in Table 11.4. It is useful for purposes of assessment and treatment planning to organize these diverse features according to the five planes of self-aware consciousness that have evolved in a stepwise manner in human beings (12). The five planes of self-aware functioning of the body can be distinguished by distinct roles in processing physical sensations (in the sexual plane), motivational drives (in the material plane), affective attachments (in the emotional plane), emotional communication and symbolization (in the intellectual plane), and subtle sentiments like awe and compassion (in the spiritual plane). The corresponding content of these planes for thought and for the psyche is described elsewhere (12), but in discussing somatizing and dissociative disorders we must focus primarily on the awareness of the body.

People with alexithymia often have personality disorders, but not all patients with personality disorders are alexithymic. In particular, patients with antisocial and borderline personality disorders are often highly alexithymic (35). More generally, scores on the Toronto Alexithymia Scale (TAS) are moderately correlated with all three dimensions of character of the Temperament and Character Inventory (TCI) (12). The strongest relations are between the TAS subscale for externally oriented thinking and the TCI scale for material aspects of self-transcendence (self-forgetfulness). Such individuals are slow to become self-aware of physical sensations (36).

People with alexithymia are also at higher risk for somatizing disorders, substance dependence, depression, and particular psychosomatic disorders, such as hypertension, irritable bowel syndrome, and fibromyalgia (28, 37, 38). For example, patients with fibromyalgia are higher in alexithymia and have greater anxiety and inwardly directed anger than healthy controls (37). Such findings suggest that alexithymics experience emotional stimuli in the normal physiological ways (e.g., tense muscles, peristaltic contractions) but are unable to identify and interpret them insightfully in self-awareness (39). Not knowing the

TABLE 11.4. Features of alexithymia grouped according to planes of self-awareness (12, 29).

Plane of awareness	Abnormalities observed in alexithymics
Sexual plane (physical sensations and fantasy)	Stiff, wooden posture
	Difficulty distinguishing between bodily and emotional feeling
	Dreams and fantasies are few, mundane, and unimaginative
	Difficulty identifying different types of feelings
	Anxiety about the significance of feelings
Material plane (motivational drives)	Lack of pleasure seeking
	Narrow, repetitive focus of interests
	Low frustration tolerance, overwhelmed by practical tasks
	Limited understanding of causes of emotions
	Difficulty describing own emotions
Emotional plane (affective attachments)	Lack of capacity for enjoyment
	Unable to appreciate beauty in art or nature
	Lack of empathy and understanding of feelings of others
	Awkward and/or detached in social relationships
Intellectual plane (emotional communication and symbolization)	Concrete, chronological thinking without emotional contextual analysis
	Lack of mindfulness about emotions of self and others
	Lack of symbolization
	Lack of achievement and creativity
Spiritual plane (sentiments)	No sentiment of awe about natural wonders and mysteries
	No sentiment of connectedness with nature or other people
	No sentiment of reverence for anything sacred
	No sentiment of unity and integration in thinking

TABLE 11.5. Experiential methods for elevating emotional intelligence in chronic somatoform and dissociative disorders, that is, of reducing alexithymia by elevating self-awareness of the body and its sensations, drives, emotions, and sentiments (Cloninger and Cloninger, 2011 (81) and the Know Yourself © well-being coaching program of the Anthropedia Foundation).

Indicators of elevated body self-awareness	Methods for elevating body self-awareness
Sexual plane	
Fluid and expressive body movement	Gymnastics and yoga
Facility identifying emotions	Expressive dance
Imaginative fantasy and dreams	Body remodeling and acupuncture
Material plane	
Broadening of interests and sources of satisfaction	Individualized healthy diet for body type and balancing cravings
Non-violent assertive communication	Compassionate communication training
Emotional plane	
Appreciation of beauty in art and nature	Experiencing beautiful artistic creations
Empathy and understanding others feelings	Active listening and empathy training
Intellectual plane	
Awareness of emotional drives and conflicts of one's self and others	Psychoeducation about temperament and conflict resolution with self and others
Intelligence in emotional problem-solving	Psychodrama and group therapy
Artistic and other creative communication	Personal engagement in communication
Spiritual plane	
Awareness of subtle sentiments and self-transcendent values:	
Awe about mysteries and wonders	
Connectedness with nature	Union with nature meditation
Abnegation of self-respect and compassion for others	Personal engagement in self-transcendent activities
Reverence for sacred things	

emotional significance or cause of the sensations, somatizing patients interpret them incorrectly as symptoms of physical illness and feel sickly. The associated distress may set up a vicious cycle or downward spiral of somatic anxiety.

Alexithymia interferes with talk therapies that require facility with uncovering and describing emotions and that are anxiety-provoking. Therefore, appropriate therapies require promotion of calmness and communication in the language of the body. Treatments of choice based on our clinical experience and available research are presented in Table 11.5 along with the corresponding target problem in chronic somatizing and dissociative disorders. Treatment recommendations are sometimes made for complex protocols in which it is unclear what is being done and for whom. Some forms of mindfulness therapy, cognitive-behavioral therapy (CBT), or eye movement desensitization and reprocessing (EMDR) are useful for some symptoms of some

somatoform patients (40–42), but it is unclear what therapeutic elements are useful for particular symptoms of particular patients. In the past treatment of somatizing patients, results have often been incomplete with much refusal of psychiatric treatment, frequent drop-out, and weak to moderate results of those retained (1, 43, 44). We have found it important, therefore, in developing and optimizing treatment methods for individual patients to relate what is done to specific target signs and symptoms, as in Table 11.5.

For example, improved fluidity and expressivity of body movements can be facilitated by gymnastics and expressive dance. Physical therapies and exercises are beneficial in randomized controlled trials of a variety of chronic somatizing disorders (43). Greater awareness of one's body and enjoyment of a healthier diet can be facilitated by individualized diets that require awareness of body type and food cravings like what has long been done in Ayurvedic medicine (45). Training in non-violent assertive communication can be explained in a concrete way to facilitate more effective self-expression (46). Methods for identifying emotion can be taught, beginning with listening to verbal and physical cues, and then learning to resolve conflicts without personal criticism or sarcasm (47). A training program has also been developed to assist well-being coaches and therapists to teach an understanding of emotional processes and specific meditations that enhance sensory awareness, appreciation of beauty, empathy, and the principles of well-being (48). The promotion of health through increased self-awareness is applicable to a wide range of people, including individuals with deficits in any form of self-awareness, including alexithymics and chronic somatizing patients.

The methods described in Table 11.5 are designed for long-term treatment of chronic patients and additional methods are needed for intervention with acute patients, such as acute conversions or fugues. The methods of Table 11.5 are focused on elevating self-awareness of the body's sensations, motivational drives, emotional attachments, emotional symbols, and sentiments. These are what we label as the components of the body that can be elevated in self-aware consciousness, bringing what has been lost down in the unconscious up into conscious self-awareness.

In contrast, the procedures recommended for acute patients are directed at what we label as the "body component of thought": namely, feelings of self-respect, self-mastery, intimacy, capacity to work through mental trauma, and the spirit of self-sacrifice. These cognitive phenomena require different treatment methods. In particular, the therapy is directed at somatic aspects of thought so the quality of therapist's relationship to the patient is crucial. Without words, the therapist must relate directly to the patient with hope, compassion, and faith while helping the patient find ways they can learn the art of living well. This quality of compassion provides appeasement, rather than provoking anxiety, frustration, or other forms of negative emotion, in both the patient and the therapist. In the context of this kind of therapeutic relationship, the patient can be helped to reconcile emotional conflicts in each realm of their life, as described in Table 11.6. When possible, graded physical exercise can be both relaxing and helpful in building self-respect and fitness, as has been shown in randomized controlled trials of patients with complaints of fibromyalgia and chronic fatigue (49). Particular somatic methods are helpful in dealing with the effects of mental trauma and stress according to randomized controlled trials; these include eye movement desensitization, cardiac coherence, supplementing diets with omega-3 fatty acids for brain fluidity, and others (50). Group therapy has been shown in a randomized controlled trial to improve physical and mental health in Somatization Disorder for at least a year after treatment (51). In addition, a meditation on Union with Nature in which a person increases their awareness of sensations from all five of their special senses is particularly useful but needs to be practiced for 30 minutes at least three times daily following mental trauma like

TABLE 11.6. Experiential methods for elevating the body component of thought in acute somatizing and dissociative disorders (e.g., conversion or fugue).

Indicators of elevated body component of thought	Treatments of choice
Feelings of self-respect	Therapist's hopeful validation
	Reconciliation of conflicts between extremes of Harm Avoidance (anxiety versus risk-taking)
	Cardiac coherence
	Physical exercise for fitness
Feelings of impulse control and self-mastery (ability to delay gratification, responsibility, purposefulness)	Therapist's forgiveness and kindness
	Reconciliation of conflicts between extremes of Novelty Seeking (impulsive versus rigid)
	Goal-setting and accomplishment
Feelings of intimacy and security in social attachments	Therapist's spiritual appeasement
	Reconciliation of conflicts between extremes of Reward Dependence (approval versus privacy seeking)
	Engagement in social activities
Retentive and flexible working memory	Therapist's non-judging patience
Capacity to work through mental trauma calmly	Reconciliation of conflicts between extremes of Persistence (perseverative versus impersistent)
	Eye movement desensitization and integration for trauma
Spirit of self-sacrifice	Therapist's integrated intelligence
	Union in nature meditation 3×/day
	Engagement in self-transcendent activities

those typically associated with acute conversions or fugues in order to allow de-stressing of the limbic system (12, 48). This meditation is a means of enhancing sensory awareness to bring satisfaction and joy from everyday natural experiences of everyday life like walking, eating, smelling, hearing, and seeing. Detailed recommendations about choice of medications that are useful for target symptoms in somatizing and dissociative disorders, such as somatic anxiety, are described in the chapter on personality disorders.

Up to now we have presented a flexible target-symptom approach to somatizing and dissociative disorders that addresses the underlying deficits in emotional intelligence because most patients will not fit neatly into specific categories as described in DSM-5. However, different clinical syndromes do have some particular features that are helpful in clarifying how to apply the general principles in a flexible manner tailored to the individual patient. Therefore, we will now consider several specific syndromes in terms of assessment, etiology, and treatment.

11.4. Somatization Disorder (Briquet's Syndrome)

Somatization Disorder is the prototype of all somatizing disorders. Its features can be predicted from the complaints expected to arise from deficits in emotional intelligence in all five of the realms of body awareness described in Table 11.4. The deficits in the sexual plane are frequently associated with distress, multiple bodily pains from a low pain threshold, and sexual or reproductive complaints. The deficits in the material plane are frequently associated with low frustration tolerance, poor impulse control leading to substance dependence and violence, and gastrointestinal complaints like irritable bowel syndrome. The deficits in the emotional plane are frequently associated with insecure social attachments, little appreciation of beauty, and emotional lability. The deficits in the intellectual plane are associated with poor emotional communication, such as being a poor historian with little understanding of emotions of one's self or others. The deficits in the spiritual plane are associated with low quality of life due to a lack of positive sentiments, which leads to a low level of integration of one's desires, goals, and values. Nevertheless, it is instructive to know how the syndrome came to be recognized and how the current understanding of Somatization Disorder developed historically.

Originally Somatization Disorder was called chronic hysteria or hysterical neurosis. Patients with hysteria are women in 95% of cases since antiquity so the name was based on the concept from ancient Greece that a wandering uterus caused pains in different parts of the body, which is now largely disproven except in cases of endometriosis. Eli Robins and Sam Guze developed the modern description of the syndrome and validated it rigorously by follow-up and family studies (52). According to their descriptions, hysteria was a chronic disorder in which patients had medically unexplained somatic complaints in nearly all organ systems, including multiple bodily pains, gastrointestinal problems, sexual or reproductive symptoms, and pseudoneurological problems (conversion reactions). The type, number, and distribution of complaints allowed reliable discrimination of patients with a predictable course of illness and characteristic family history, whereas diagnosis and prognosis were unreliable when based on isolated complaints or severity of subjective distress. Young adult women usually presented with the disorder and their course was chronic, although the specific symptoms varied in location and intensity in response to the vicissitudes of their chaotic lives. The patients had poor affective regulation, were notoriously poor and inconsistent historians, and had little awareness of the relations between the personal and social stresses in their life and their physical complaints. As a result of the patient's prominent deficits in emotional intelligence, some people suggested the patients were throw-backs to an earlier point in the evolution of human consciousness. Their way of thinking appears more typical of people who lived about 3000 years ago than it is of the consciousness of contemporary human beings.

Guze carried out blinded follow-up and family studies that showed that patients with this syndrome had a chronic course but were not at increased risk for medical disorders. Studies showed that antisocial personality disorder and hysteria often occurred together in the same individuals as well as in the same families (53).

Most patients and some psychiatrists disliked the use of the term hysteria because it was rather pejorative and also ambiguous. A French psychiatrist named Briquet had described a similar group of patients with multiple somatic complaints (54), so Guze suggested the label of Briquet's syndrome in order to distinguish the syndrome from histrionic personality disorders and acute conversion reactions. Guze's criteria were well validated but were cumbersome, requiring endorsement of over 20 out of 59 possible symptoms of Briquet's syndrome, distributed in at least nine of ten empirically derived groups. As a result, few people used the research criteria in clinical practice.

The widespread nature of the syndrome and its heritability were confirmed in adoption studies conducted in Sweden (55). Somatizing disorders were also shown to be the major cause of all absenteeism from work, thereby causing great economic loss to society as well as individual suffering. The adoption studies also confirmed the genetic overlap in the causes of somatizing disorders and personality traits associated with criminality, such as antisocial and borderline personality disorder.

In 1980 the term Somatization Disorder was adopted in DSM-III, which tried to be strictly descriptive, not to make etiological assumptions, and to avoid all eponyms. The criteria for diagnosis were simplified but remained lengthy and little used. For DSM-IV, Cloninger developed the DSM-IV criteria using the same methods he had developed in the Swedish adoption studies (4).

The criteria were designed to be easy to remember and use: at least four bodily pains, two gastrointestinal complaints, one pseudoneurological symptom, and one sexual or reproductive symptom. If any one of these requirements were not met, the diagnosis cannot be made so inquiry can stop at that point. The criteria for Somatization Disorder identified essentially the same patients as the original criteria of Guze. The high sensitivity and specificity of the criteria were confirmed in DSM-IV field trials at multiple independent sites, including psychiatric and primary care populations (4). As a result, practical criteria are now available for the diagnosis of Somatization Disorder.

Medical specialists with little knowledge of psychiatry often conclude that patients with Somatization Disorder have fibromyalgia and irritable bowel syndromes. Such diagnoses by medical subspecialists reflect their special interests and do not explain the full somatization syndrome, the prominent and widespread deficits in emotional intelligence and character development, or genetic association with impulsive personality disorders. Furthermore, treatment of the complaints of fibromyalgia and irritable bowel syndrome often involves the use of psychotropic medications and cognitive-behavioral treatments. Primary care physicians and medical specialists often play prominent roles in managing the lives of patients with Somatization Disorder, and there should always be collegial communication among their various physicians. Even when the goal is merely management of a chronic condition, it is useful for all of a somatizing patient's physicians to be educated about the nature and scope of the underlying disorder. However, if a patient is really interested in getting well, then they require treatments addressing the underlying causes of their complaints. Accordingly, comprehensive treatment of patients with Somatization Disorder requires a specialist in psychiatry to deliver the psychiatric care and coordinate the various facets of treatment in consultation with other specialists. Which physician is the overall supervisor will depend on the patient's therapeutic relationships and most prominent problems. Such coordinated care can work very well even with the most difficult of patients (1).

Unfortunately, general medical practitioners in busy practices who spend only a few minutes with each patient have found it challenging to apply the full diagnostic criteria for Somatization Disorder, even though the criteria can be efficiently screened in a stepwise manner. Many somatizing patients present in primary care settings so to accommodate the needs of primary care physicians, DSM-5 has introduced a new category called Somatic Symptom Disorder, even though this diagnosis has doubtful validity, as we will discuss later. The diagnosis of Somatization Disorder was dropped from DSM-5 despite strong evidence of validity and a rich history. Accordingly we recommend that clinicians who wish to practice on the basis of scientific evidence should continue to use the well-validated DSM-IV criteria for Somatization Disorder and not use the unvalidated DSM-5 criteria for Somatic Symptom Disorder.

Traditional ways of treating Somatization Disorder begin with particular attention to the way the diagnosis and a therapeutic alliance are established. Patients with SD are reassured when their physician takes the time to collect a thorough history, obtains past medical records, and obtains collateral information from family members with informed consent. Such careful documentation often corrects inconsistencies and omissions, avoids the need to repeat medical tests, and communicates the respect of the therapist for the dignity and past suffering of the patient. Comorbid conditions, such as disorders of personality, mood, and substance abuse, are common and may require treatment also. It is useful to assess personality with a questionnaire with internal validity controls, such as the Temperament and Character Inventory, particularly since this is prescriptive of treatment targets, as described in the chapter on personality disorders. This helps to focus patients on their active role in developing a healthy life by developing greater self-awareness and beginning on the path to their well-being. No one can be forced to become more self-aware, so there is a wide range of possible goals. The possible goals include at least education to help reduce excessive health care utilization and exposure to unnecessary tests and procedures, as is often done by providing consultation to their primary care physician (56). It can also include pharmacotherapy for target symptoms of somatic anxiety, depression, impulsivity, emotional detachment, and cognitive distortion, as described in the chapter on personality disorders. For example, as adjuncts to psychotherapy, antidepressants may be useful for anxiety and mood symptoms, mood stabilizers for impulsivity, and atypical antipsychotics for emotional detachment and/or cognitive distortion (43). Cognitive-behavioral therapy has been recommended as a treatment of choice based on a meta-analysis of 29 randomized trials, but the effects were only moderate: symptom severity was reduced in 71% of cases but functional status was only improved in 26% (57). A later randomized trial of CBT showed that it can produce moderate but clinically meaningful reductions in health care utilization and subjective complaints for about a year after treatment, even though it does not correct underlying deficits in emotional intelligence (58). However, relapse and recurrence are major problems for treatments like CBT that do not correct the underlying deficits in emotional intelligence of patients with somatizing disorders (59). More ambitious work, still unproven by randomized controlled trials, includes efforts focused on the habilitation of emotional intelligence as described earlier.

11.5. Somatic Symptom Disorder in DSM-5

The contributors to DSM-5 recognized that it requires time and skill for a physician to determine whether a patient's complaints are medically explained or not, as was required for the diagnosis of somatoform disorders in DSM-III and -IV. However, the contributors to DSM-5 failed to appreciate that it is even more difficult for physicians to judge whether a person's subjective

distress is excessive. The proposed criteria for Somatic Symptom Disorder in DSM-5 require only that a clinician judges a person's distress about one or more physical complaints to be excessive or disproportionate in order to label them with the diagnosis of a mental disorder. Unfortunately this criterion still requires a clinician to judge whether the patient's complaints can be medically explained or not. It is even more problematic that in DSM-5 there are no restrictive criteria about the underlying pathophysiology or about the number, type, or duration of the complaint. Duration is noted to typically be 6 months or more, but this is not required. Likewise, there is no exclusion based on presence of other disorders, except that it is noted in the text that the diagnosis should not be made when the somatic complaints only occur during episodes of depression. Overall, these broad criteria are dangerously over-inclusive; this diagnosis alone would result in 8% of people in the general population being labeled as mentally ill on the basis of a clinician's subjective judgment that their complaints are excessive (60). These criteria are clinically simplistic, superficial, and are not justified by scientific evidence as needed for a valid diagnosis. They do not avoid any of the problems of mind–body dualism that its well-intentioned but ill-informed proponents suggest.

The emphasis in DSM-5 is on the diagnostician's subjective judgment that a person's thoughts, feelings, and behaviors are excessive or disproportionate to the seriousness of their somatic symptoms. Such subjective judgments can be made with strong reliability (60, 61) and still be invalid because they depend on many untested or untestable assumptions about the etiology and motivation (62, 63) and occur in large numbers of people with little or no psychopathology or persistent disability (64, 65). For example, more than one in three patients with no mental disorder in primary health care complain of excessive fatigue or pain (65). The choice of the APA to broaden these criteria is a regression to diagnostic approaches that were discredited in the mid-20th century in Europe and the United States, as illustrated by the previously mentioned research of Robins and Guze. The APA criteria for Somatic Symptom Disorder have no demonstrated utility for informing etiology, prognosis, or treatment. The course of a patient's subjective distress depends on the underlying psychiatric syndrome, personality profile, and complex interactions between a person's psychobiological strengths and situational stressors that are not measured by the suggested APA criteria. Hopefully, responsible physicians will ignore the ill-advised criteria proposed by the APA, which actually do not have any compelling scientific or legal force.

Even when there are multiple unexplained somatic complaints, there is little information about prognosis and treatment because of the heterogeneity of the patients. A meta-analysis of 34 trials of patients with multiple somatic complaints reviewed the relations of outcome to diagnosis (chronic fatigue versus irritable bowel versus fibromyalgia versus somatization), treatment (CBT versus relaxation versus exercise), and format of treatment (individual versus group) (66). Treatments did provide modest benefits compared to controls, but there was no differential effect of diagnosis or type of treatment.

In DSM-5, pain disorders are grouped together with Somatic Symptom Disorder, but are distinguished by a specifier "with predominant pain." Because DSM-5 criteria for Somatic Symptom Disorder lack validity, we will henceforth ignore it. Pain disorders will be considered separately because of their distinctive clinical features.

11.6. Conversion Disorders

A conversion disorder is a medically unexplained loss or alteration in voluntary sensori-motor functions. The term "conversion" implies that a psychological stressor is being expressed involuntarily as in the language of the body as a functional neurological symptom. Accordingly, in DSM-IV there was a requirement for documenting a psychological stressor that triggered the symptoms. However, sometimes information about the stressor is not declared or known consciously, so in DSM-5 there is no requirement to document a psychological stressor, which would require getting to understand the patient thoroughly. Instead in DSM-5, the diagnosis of Conversion Disorder is based on demonstrating that the complaint is not compatible with recognized neurological or medical conditions on the basis of rigorous neuropsychiatric examination. Therefore, in DSM-5, conversion disorders may also be called "functional neurological symptom disorders." However, it is a fundamental logical error to assume that the absence of a neurological explanation implies the presence of a psychiatric disorder. Proper diagnosis of a conversion disorder requires an understanding of the whole person, including the functioning of their neurological system in its biopsychosocial context.

The classic examples of conversion disorders are sensorimotor abnormalities that mimic neurological disorders, so they often require coordinated evaluation and treatment with neurologists and other medical specialists (1). These deficits include loss of the special senses of sight, hearing, smell, taste, and touch. Alterations of these sensory functions, such as double vision, can also be conversion disorders. Any of these deficits or disturbances of the special senses are specified in DSM-5 as a conversion disorder "with special sensory symptom."

Other common examples of conversion disorders are specified as "with weakness or paralysis", "with abnormal movement" (e.g., tremor, dystonic movement, myoclonus, gait disorder), with swallowing symptoms, with speech symptom (e.g., dysphonia, slurred speech), with attacks or seizures. Such conversions are usually called "psychogenic movement disorders" in neurology (1). These motor deficits include psychogenic tremor or shaking, psychogenic dystonia, impaired coordination or balance, ataxia or gait disturbance (e.g., astasia–abasia), functional paralysis or localized weakness, psychogenic Parkinsonism, difficulty

swallowing, aphonia, or urinary retention. In movement disorder centers, tremors are the most common psychogenic movement disorders (40%) followed by dystonias (31%) (67). The classic conversion symptom of globus hystericus is usually described as a "lump in the throat" that makes swallowing uncomfortable or difficult. The classic conversion symptom of astasia–abasia is the inability to stand or walk in a normal manner. The gait is bizarre and not consistent with a specific neurological lesion; for example, often the patient sways wildly and nearly falls, but recovers at the last moment.

Patients also frequently present with Conversion Disorder with seizures or seizure-like attacks. Such conversions are usually called "pseudoseizures" or "psychogenic non-epileptic seizures" (PNES) by neurologists (1). Many patients with recurrent seizures confirmed by electroencephalograms also have some pseudoseizures, so the diagnosis of such patients can be challenging. The key distinction is that conversion disorders involve some voluntary sensori-motor signs and symptoms mimicking a seizure (67).

Still other people present symptoms of more than one category of conversion and are designated as "Conversion Disorder with mixed symptoms" in DSM-5. Some patients have exaggerated behaviors during the later phases of a startle response, as in Latah, but these syndromes are usually classified among the culture-bound disorders.

There are no specific laboratory tests or signs on physical examination that are diagnostic of conversion disorder. As a result, the differential diagnosis of conversion disorder or a general medical condition requires knowledge of both psychopathology and general medicine. Efforts are made to detect psychopathology or associated psychological factors, as well as alternative medical explanations. Psychopathology can coexist with other medical disorders, as when individuals with epilepsy also present pseudoseizures on occasion. Also chronic conversion disorders can lead to atrophy or contractures or other physical lesions from long-term disuse. Conversion disorders should *never* be based only on exclusion of known medical disorders. What physicians know is finite and it is an error of logic to assume that the absence of proof is the proof of absence of a physical cause. Therefore, in DSM-IV the diagnosis of Conversion Disorder required positive evidence of psychological factors that are judged to be associated with the medically unexplained symptom or deficit. The reliance on only inconsistent neurological signs without any requirement of psychological disturbance is expedient but questionable; best practice would be to require both evidence of a close relationship between psychological stress and functional neurological disturbance, which is what is actually observed clinically in valid cases (1).

The etiology of conversion disorders and dissociative disorders is an area of rapidly growing knowledge from recent work in functional brain imaging. Hyperactivity of the anterior cingulate cortex (ACC) is found in most, but not all, studies of conversion and dissociative disorders, usually along with either increased or decreased activity of the dorsolateral prefrontal cortex. The ACC is an interface for emotional regulation, motivation, and motor processing to determine an appropriate motor response, as discussed earlier. For example, hyperactivity of the ACC has been suggested to actively inhibit motor activity in psychogenic paralysis (68). Hence treatments are directed acutely at emotional appeasement of the emotional brain, as described earlier. The methods that have been used effectively for acute interventions include hypnosis, interviews concomitant with sedative injections (usually amytal or lorazepam), or other forms of reassurance and relaxation. Such interventions can lead to a dramatic catharsis with rapid relief of the symptoms. Then further treatment can be carried out as suggested earlier in this chapter to reduce stressors and to understand and mitigate the underlying vulnerability to the symptoms. Practical advice on implementation of such methods has been presented in detail (1, 44).

11.7. Other Somatic Symptom Disorders

The somatoform cluster in DSM-IV included a heterogeneous collection of disorders, including pain disorders, hypochondriasis, body dysmorphic disorder, and others like pseudocyesis that are not otherwise specified. The somatizing conditions recognized in DSM-IV involve diverse mechanisms and principles and some are unrelated to Somatization Disorder. As a result, we will focus mainly on differential diagnosis with brief comments about etiology and treatment.

According to DSM-IV, if the chief complaint or predominant focus of the patient is pain, the diagnosis of Pain Disorder should be considered. In DSM-5 Pain Disorders are grouped under Somatic Symptom Disorder and specified as "with predominant pain". In view of the inadequacy of DSM-5 criteria, the diagnosis of pain disorder can be based on DSM-IV criteria for pain disorder when there is need for reliability and validity, as in disability evaluations. Specifically, pain is the predominant focus of the presentation, causes clinically significant distress or impairment, and psychological factors are judged to have an important role in the onset, severity, exacerbation, or maintenance of the pain. A mental disorder is diagnosed only if the pain disorder is associated with significant distress or impairment from psychological factors, or if it is associated with both psychological factors and a general medical condition.

Pain disorders are heterogeneous, and are often comorbid with other physical and mental disorders. As a result it is important to identify the underlying psychopathology and any associated stressors. Once this is done, there are many patients with pain disorder who are alexithymic, which predisposes to complaints about pain (31, 69). In these pain patients, the same treatment approach is indicated as described earlier for improving emotional regulation in alexithymics.

Body Dysmorphic Disorder (BDD) involves the preoccupation with an imagined or slight defect in appearance. Preoccupation with the skin, hair, and nose are the most common, but any body area can be the focus of concern. Patients with BDD often can be observed to pick their skin, check their appearance in the mirror frequently, or to try to camouflage their appearance with a hat or make-up (70). These patients often seek cosmetic surgery repeatedly, only to remain dissatisfied with their appearance. Nearly half of the patients are delusional, particularly having delusions of reference (71). BDD is associated with severe anxiety and frequent suicide attempts. Clinically it appears to be more closely related to social phobia and obsessive-compulsive disorder than to Somatization Disorder. Patients are usually able to describe their emotions well, even though they are socially phobic, obsessive, and rejection-sensitive. Serotonergic antidepressants and cognitive-behavioral therapy like that used for social phobias and OCD is frequently effective in the treatment of BDD.

Hypochondriasis is the preoccupation with unrealistic fears of having a disease, or the belief that one has a disease. This fear or idea persists despite medical reassurance and lasts more than 6 months. Patients with hypochondriasis are typically fearful and anxiety-prone, reacting quickly and strongly to sensory stimuli. Until the late 19th century, hypochondriasis was associated specifically with complaints involving the "hypochondriac" region of the abdomen – that is, below the costal cartilages—rather than with regionally non-specific morbid disease preoccupation (55). Hypochondriasis is called Illness Anxiety Disorder in DSM-5. The DSM-IV and DSM-5 criteria are essentially the same as proposed by Gillespie in 1928,who believed that hypochondriasis was an independent, discrete disease entity (72). Others concluded that hypochondriasis was always a secondary part of another syndrome, usually a depressive disorder (73). More recent studies confirm that patients with hypochondriasis frequently have other co-occurring mental disorders, particularly anxiety and depressive disorders.

Hypochondriacs have an increased past history of serious childhood illnesses and experience with disease in family members. These patients are often highly verbal and aware of their emotional processes, but are easily triggered to anticipate the worst. Adoption studies have identified hypochondriacal patients who are harm avoidant and have fewer biological relatives with criminality; this is in direct contrast to somatizing patients who have an increased risk of biological relatives with criminality (74). Essentially hypochondriasis is a disorder of phobic anxiety, rather than a deficit in emotional awareness. Accordingly, the recommended treatments of choice are similar to those for anxiety and mood disorders, such as serotonergic antidepressants, cognitive-behavioral therapy, or psychodynamic therapy. In DSM-5, hypochondriasis is classified with both anxiety disorders and somatic symptom disorders.

11.8. Dissociative Disorders

Dissociative disorders involve the disruption or loss of the integrative mechanisms of consciousness, memory, identity, or perception. These disruptions may be sudden or gradual, and transient or chronic. Dissociative disorders include amnesia, fugue, depersonalization, and dissociative identity disorder (formerly called Multiple Personality Disorder). There are no major diagnostic changes for dissociative disorders between DSM-IV and -5, except that DSM-5 excludes states of possession that are recognized as a normal part of cultural or religious practice. Dissociative amnesia is a disruption of memory: specifically, it is the inability to recall important personal information in excess of what can explained by ordinary forgetfulness. Dissociative fugue is a disruption of identity: it involves the sudden travel away from home and work, accompanied by inability to recall personal identity or at least the assumption of a new identity. Depersonalization Disorder is a disruption of perception: it involves the feeling of being detached from one's mind or body, as if they can be observed from a distance. Dissociative identity disorder (DID) is a disruption of consciousness and identity. Two or more distinct identities or personality states recurrently take control of the individual's behavior in DID, and the person is unable to recall important personal information about their other states. It involves the fragmentation of identity, rather than the possession of multiple personalities that are each complete but separate, so the name has been changed to DID, rather than multiple personality disorder, to correct this popular misconception. Transitions between personalities or the onset of amnesic or fugue states is usually precipitated by psychosocial stress, such as marital quarrels, personal rejection, or events associated with a high risk of injury or death. Early childhood abuse is often a predisposing factor (75). Thus both conversion and dissociative disorders are typically precipitated by severe psychosocial stress, but it is often difficult to elicit the relevant history before treatment until the clinician can contact collateral informants. Caution and restraint is required for the clinician to avoid iatrogenic suggestion of false memories and identity disturbances in patients, as illustrated in the infamous example of Sybil (76–78).

DSM-5 is careful to distinguish DID from states that are considered normal expressions of particular religious or cultural practices in which a benign spirit is believed to have taken temporary possession of a person. The approach taken in DSM-5 (i.e., to distinguish DID from states accepted as culturally normal) leaves the decision about what is normal to a person's subculture or religion of choice. This exclusion still allows inclusion of possession states as cases of DID when possession states impair a person's functioning or cause distress, as in cases where a person seeks exorcism.

DID and Somatization Disorder are both chronic conditions, so they are sometimes grouped together as chronic hysteria. Likewise, conversion disorders and dissociative amnesia, fugue, and depersonalization are often acute in onset and brief in duration, so they are sometimes grouped together as acute hysteria (68). The separation of somatoform and dissociative disorders is artificial because many patients present with combinations of somatization, conversion, and dissociation, as is typical of patients with Somatization Disorder. Furthermore, functional neuroimaging results confirm the utility of groupings based on course; acute hysteria, whether a conversion or dissociative disorder, is most consistently associated with hyperactivation of the anterior cingulate cortex (68). Essentially, stress activates the limbic system and the anterior cingulate cortex serves as an interface to regulate a wide variety of aspects of motor activity (e.g., seizure or paralysis in conversion disorders or runaway in dissociative fugue), perception (e.g., detachment in depersonalization or blindness, deafness, or anesthesia in conversion), or consciousness and identity (seizure-like trance states in conversion disorders or new identities in dissociative disorders).

Before functional imaging was possible, detailed clinical studies of patients with conversion and dissociative disorders were a major impetus to the development of psychodynamic concepts by Janet and Freud. Both men thought that the development of hysterical symptoms was the result of disturbing mental associations becoming unavailable to consciousness by voluntary recall. Janet proposed that hysterical symptoms could arise when forces that normally serve to integrate mental function fail and some functions escape from active central control. This theoretical process was referred to by Janet as dissociation (79). In contrast, Freud suggested that there was an active process by which disturbing mental associations were removed from conscious awareness (80). This active process of inhibition or removal from availability to voluntary recall was called repression. Repression was conceived as a mechanism to protect the patient from emotional pain arising from either disturbing external circumstances or anxiety-provoking internal urges and feelings. The theoretical formulation of Freud is remarkably well supported by contemporary findings from functional brain imaging; in fact, hyperactivity of the anterior cingulate cortex in response to stress can actively inhibit motor activity, sensory perception, and conscious recall of unpleasant events or even one's identity (1).

The recent progress in the assessment, etiology, and treatment of patients with somatoform and dissociative disorders offers encouragement to clinicians and neuroscientists alike that modern psychiatry is a clinical field that integrates the neurobiological and psychosocial sciences with compassion and respect for human dignity. The complexities of somatizing and dissociative disorders are mysteries that continue to stimulate an ever-deeper appreciation of the wonders of human nature.

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12
Anorexia Nervosa and Bulimia Nervosa

Scott J. Crow, M.D. and Elke D. Eckert, M.D.

Abstract The most widespread eating disorders, AN and BN, are potentially serious disorders with high morbidity and mortality primarily affecting young females. The disorders are related; often there are no clear boundaries between the two disorders. Recent advances have been made in defining the interplay of risk factors leading to the disorders. These include various biologic and genetic factors, such as personality and comorbid psychiatric symptoms. Although there have also been advances in the treatment of the disorders, much more research is needed, particularly in AN, to define effective treatments.

Keywords Anorexia · Bulimia · Eating disorders · Binge-purge · Binge eating

12.1. Etiology and Pathogenesis

An eating disorder can be defined as a persistent disturbance of eating behavior and/or a behavior intended to control weight which impairs social function or physical health significantly but is not due to a medical or other psychiatric disorder. The most widely recognized eating disorders, AN and BN are common, potentially serious disorders that primarily affect young females. Both disorders are characterized by peculiar attitudes and behaviors directed toward eating and weight accompanied by intense weight gain. AN is further characterized by obsessive pursuit of extreme thinness leading to emaciation and disturbance of body image. One important change to the AN criteria in DSM-5 is that the amenorrhea criterion from DSM-IV has been eliminated.

The cardinal feature of BN is eating binges which are powerful and intractable urges to consume large amounts of food over a short time. Usually, this is followed by either self-induced vomiting or ingestion of laxatives in an attempt to prevent weigh gain. However, BN does not produce the emaciation which accompanies AN. The only change to the BN criteria for DSM-5 is that the required frequency for binge-eating and purging is reduced from twice to once per week.

Although AN and BN are separate diagnostic disorders, there are no clear boundaries between the two conditions. Not only can the one develop from the other, but characteristics of both disorders are frequently present together in the same individual. Also, there are similarities in many of the important characteristics of the disorders (see Table 12.1).

The specific etiology of AN and BN is elusive and still unknown, although the genesis appears to be multifactorial, with the vulnerability to AN and BN arising from interplay of genetic, biologic, psychological, and environmental risk factors. Earlier psychological theories centered mostly on phobias and psychodynamic interpretations. One view was that AN can be seen as an eating or weight phobia; regardless of the initial stimulus for dieting, eating or weight gain begins to generate severe anxiety, while failure to eat or weight loss serves to avoid anxiety (1). Crisp (2) has postulated that a weight phobia springs from an

S.J. Crow, M.D. (✉)
Professor, Department of Psychiatry, University of Minnesota School of Medicine, Minneapolis, MN, USA
e-mail: crowx002@umn.edu

E.D. Eckert, M.D.
Professor, Department of Psychiatry, University of Minnesota School of Medicine, Minneapolis, MN, USA
e-mail: ecker001@umn.edu

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TABLE 12.1. Comparison of important clinical features of AN and BN.

Important features for AN	Important features for BN
Significantly low body weight[a]	Weight maintenance in normal range[b]
Intense fear of weight gain[a]	Intense fear of weight gain[a]
Peculiar food handling (*may* include recurrent binge–eating)[c]	Peculiar food handling (*must* include recurrent binge-eating)
Severe self-inflicted behaviors directed toward weight loss (*may* include vomiting, laxative or diuretic abuse)	Severe self-inflicted behavior directed toward weight loss (e.g., laxative or diuretic abuse, or excessive exercise or fasting)[a]
Disturbance of body image or overconcern with body shape and weight[a, d]	Overconcern with body shape and weight[a]
	Menstrual irregularities

Adapted from American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, Washington. APA.
[a]Required for the diagnosis according to DSM-5.
[b]A minority of BN are above normal and some are below normal weight range.
[c]In DSM-5, AN is subtyped into binge-eating/purging and restricting subtypes.
[d]In DSM-5, denial of the seriousness of the low weight may substitute for this criterion.

avoidance response to the sexual and social demands of puberty. Bruch (3) described early false learning experiences as causing disturbance in body image, disturbance in perception, and, in turn, lack of recognition of hunger, fatigue, and weakness.

12.1.1. Environmental Factors

Many of the same environmental factors that predispose to the development of AN are risk factors for BN. Socio-cultural theories have pointed to a shift in cultural standards for feminine beauty toward thinness (4). This cultural ideal may indirectly contribute to the development of AN and BN, particularly among vulnerable adolescents, who equate weight control and thinness with beauty and success. A recent study examined influences of socio-cultural effects by studying the incidence of AN in Curacao, a society undergoing a socioeconomic transition (5). The overall incidence of AN was much lower than in the United States or in the Netherlands, and the authors found that socio-cultural differences within the island were related to AN. The majority population on this island is black, and no cases of AN were found in this segment of the population, in which, interestingly, being overweight is socially more accepted than in the white and mixed population segment on this island. Many of the white or mixed cases who had AN had been more exposed to high income western cultures. The incidence of AN among the white and mixed-race Curacao population (9.1 per 100,000 person-years) was similar to the incidence in the United States and the Netherlands.

Other environmental factors have been identified as contributing to eating disorders, particularly BN. Although early reports suggested a specific association between bulimia and a history of sexual abuse, since it does occur with some frequency in BN patients, this apparent association is not specific to BN, but rather a nonspecific risk factor for psychiatric illness in later life (6). Some data does suggest that early sexual trauma may contribute to a worsened course and greater comorbidity in BN (7). Other data suggests some differences in early experiences occurring in AN and BN. For example, critical comments by family about eating, weight and shape have been found as more prevalent in BN compared to anorectics (8).

12.1.2. Biologic factors

Although psychosocial factors may be significant risk factors, arguments for a biological vulnerability include the fact that despite the emphasis on thinness in industrialized countries the world over, only a small percent of females develop eating disorders. Also, descriptions of AN go back to the 19th century, long before there was an emphasis on thinness.

12.1.2.1. Neuroendocrine Factors

Early neuroendocrine theories for AN were based on the observation that amenorrhea and disturbed hypothalamic thermoregulation are independent of emaciation in AN, and thus Russell (9) proposed that hypothalamic dysfunction contributes to the disorder. Neuroendocrine alterations in AN are common, and controversy on the pathogenesis of these changes continues (10–12). Many of these changes relate directly to weight loss. These include alterations in TSH response to TRH, in resting gonadotropin levels and luteinizing hormone (LH) responses to provocative stimuli. Other hypothalamic disturbances, such as plasma growth hormone, T_3 and reverse T_3 directly relate to caloric restriction, since they respond rapidly to food (carbohydrate) intake before significant weight changes can occur. Some changes, including increased cortisol production and an immature pattern of LH, are probably mostly related to weight loss. Thus, although the possibility of an underlying hypothalamic abnormality remains, it appears likely that activation of the hypothalamic-pituitary-thyroid axis is precipitated by weight loss. Factors such as amount of exercise, relating to a high incidence of amenorrhea in runners and ballet dancers (13, 14), and emotional distress, perhaps relating to the elevated cortisol production rate, probably play a role.

Recent work has examined the impact of neuroendocrine factors on the expression of heritable risk for disordered eating. This line of work has shown that pubertal stress (likely reflecting ovarian hormone state) critically impacts monozygotic twin concordance for disordered eating (15). In other twin analyses the degree of disordered eating among dizygotic twins is related to both the subject's and co-twin's gender. These findings are hypothesized to relate to intrauterine testosterone exposure, with higher degrees of exposure thought to provide a protective effect (16).

12.1.2.2. Neuropeptide Factors

More recently, research has focused on the possible role of neuropeptide abnormalities resulting in disruption of normal feeding and altered appetitive drive as contributing to the etiology of eating disorders. Patients with AN and with BN do behave as if their satiety and control of eating mechanisms are deranged. Anorectic patients, compared with normal controls and those with BN endorse lower hunger ratings and higher fullness ratings in response to test meals (17). In contrast, BN patients eat significantly more food and rate their hunger afterwards as higher and their fullness as less than non-eating disordered controls when provided meals in laboratory settings (18). An extensive body of animal research has shown that satiety is determined by post-ingestive events in the upper gastrointestinal tract, and a number of abnormalities relative to satiety and post-ingestive events have been found in BN patients. Cholecystokinin, a peptide secreted by the gastrointestinal system in response to food intake, transmits satiety signals to the brain by way of vagal afferents. Post-prandial release of cholecytokinin was found to be abnormally low in BN patients (19), while in anorectics, some studies found elevations of basal levels of cholecytokinin (20). Other abnormalities relative to satiety in BN include enlarged gastric capacity (21), delayed gastric emptying (22), impaired gastric relaxation (23), and even abnormalities in functioning of the vagus nerve (24). Other neuropeptides, including beta-endorphin, neuropeptide Y, peptide YY, vasopressin, ghrelin, insulin, pancreatic polypeptide, gastric inhibitory peptide, glucagon-like peptide 1, glucagon, gastrin, orexin, and leptin have been investigated in AN and bulimia with variable results (11, 25, 26). Although these abnormalities in anorectics usually tend toward normality with weight recovery, there is evidence that leptin levels (which are normally positively correlated with body fat mass in individuals across a broad range of weight), may be higher than expected in anorectics based on the extent of weight loss, and that with weight recovery, leptin levels may prematurely normalize, leading to difficulties in achieving and sustaining a normal weight (27, 28).

12.1.2.3. Neurotransmitter Changes

Extensive work has examined the possible role of neurotransmitters in eating disorders (29, 30). A central challenge in such work is disentangling the effects of starvation from primary illness mechanisms. Barry and Klawans (31) proposed that increased dopaminergic activity may account for major signs and symptoms of AN, specifically, anorexia, hyperactivity, decreased libido, and a morbid fear of becoming fat. Altered dopamine activity has been found in both low weight and weight recovered anorectics (32, 33). Using Positron Emission Tomography (PET) to assess dopamine D2/D3 receptor binding, a recent small controlled study of weight-recovered anorectics found increased receptor binding in the antero-ventral striatum in the anorectics, and receptor binding in the dorsal caudate and dorsal putamen was positively correlated with harm avoidance (32). Although the data lends support to the possibility that dopamine changes could contribute to the characteristic harm avoidance or increased physical activity found in anorectics, much work still needs to be done to assess the role of dopamine in eating disorders. One potential approach is the use of animal models of disordered eating (34–36). For example, a model for AN has been employed that involves obsessive wheel-running in calorie-restricted mice (the activity-based anorexia model). This model is now being used to study potential medication interventions (37).

Much attention has recently been given to the role of serotonin in the eating disorders, both in human and animal studies (34). Those with AN and BN have been found to have alterations in 5-HT metabolism. Reduced basal levels of CSF 5-HIAA have been found during the acute low weight phase of the illness in anorectics compared to controls, and since the levels have been found to normalize with weight gain, it is thought that the low levels during the acute illness is a consequence of starvation (32, 38). However, levels of CSF 5-HIAA have been found to be elevated in long-term recovered anorectics (38), leading to the possibility that there may be a trait serotonin abnormality which predisposes one to the possibility of AN. Since increased serotonin activity has been implicated in obsessive and anxious individuals, it is also possible that this altered serotonin activity in weight recovered anorectics may contribute to their persistent symptoms of perfectionism, obsessiveness, and anxiety. It could be that in anorectics, dieting reduces the serotonin levels and hence protects them from the anxiety they experience with weight gain. Evidence of serotonin dysfunction (CSF 5-HIAA and indirect probes for serotonin) also occurs in BN, both during the acute symptomatic phase (39) and after symptom recovery (40), but since dieting itself can affect serotonin (41), we cannot conclude that serotonin abnormalities predate the illness. It could be that dieting provides a potential mechanism by which women, who are vulnerable for other reasons, develop eating disorders. Further evidence of a serotonergic component to BN comes from the fact that in multiple placebo-controlled double-blind studies using serotonergic antidepressants to treat those with BN, there is a significant reduction in binge-eating and purging behavior, even in BN subjects who are not depressed (42).

Using selective neurotransmitter radioligands with PET, studies confirm altered 5-HT neuronal pathway activity in AN subjects. Compared to controls, recovered restricting AN subjects have been found to have reduced 5HT2A activity in the amygdala and hippocampus, as well as in cingulate, sensorimotor, and occipital/parietal cortical regions (43). Additionally, recovered AN subjects have increased 5HT1A receptor activity in the pre-synaptic raphe nucleus and cortical-limbic-striatal post-synaptic receptors (43). Since 5HT1A post-receptor binding in many cortical areas was positively correlated with trait anxiety and harm avoidance in AN, these findings support the possibility that these alterations might contribute to increased anxiety, a common premorbid trait in AN, and hence also to vulnerability for the development of eating disorders.

12.1.2.4. Structural/Functional Brain Changes/Imaging Studies

Neuroimaging work in the field of eating disorders focused first on looking for gross structural/alterations in brain morphology, especially in the setting of starvation. Over time, this work has evolved toward functional imaging studies, initially examining activation in select regions, but increasingly now examining neural circuit function. Structural brain imaging studies have confirmed that low-weight AN is associated with enlarged ventricles and widened sulci (44) (see Fig. 12.1). Although these alterations appear to be at least partly reversible with weight restoration, some data suggests that changes may persist after recovery (45). MRI technology has used methods to determine volumetric gray and white matter alterations in AN and BN. A recent meta-analysis of such studies found that individuals with AN may have decreased gray matter volume, while those with BN may have increased gray matter (46). Such differences may normalize with clinical recovery.

Initial work examined perfusion in individuals with low-weight AN and found hypoperfusion, which appeared not always to normalize with recovery (47–50).

Stimulus processing in AN has recently been studied using fMRI. For example, people with AN, compared with healthy controls, showed a significantly greater signal response in the emotion-processing regions after viewing images of food (51). Extensive

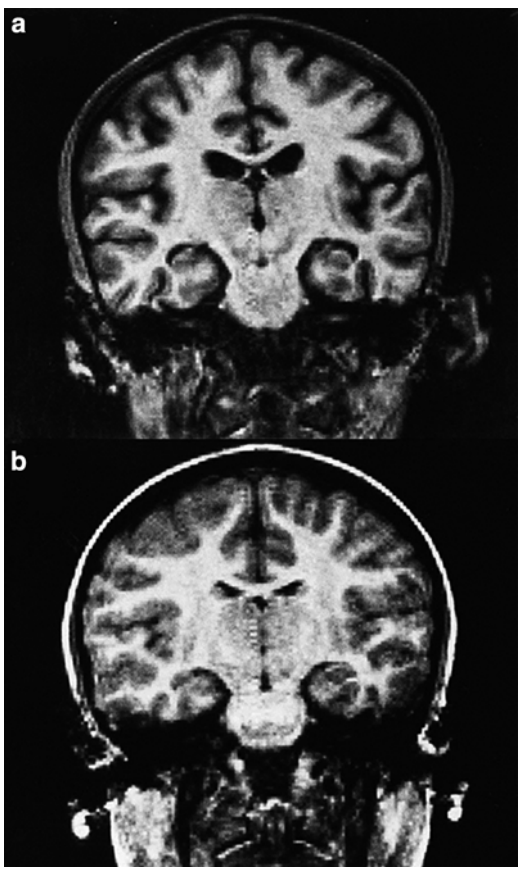

FIGURE 12.1. Coronal MRI image of an 11-year-old patient with anorexia nervosa (**a**) compared with that of an 11-year-old healthy control subject (**b**). (**a**) Sulcal enlargement and marked dilation of the third and lateral ventricles. (**b**) Normal anatomy at the same level. Reprinted from Golden NH, Ashtari M, Kohn MR, Patel M, Jacobson MS, Fletcher A, Shenker IR. Reversibility of cerebral ventricular enlargement in anorexia nervosa, demonstrated by quantitative magnetic resonance imaging. J Pediatrics 128(2), 296–301, Copyright (1996), with permission from Elsevier.

work has now examined the neural correlates of distorted body image (52). This work has generally used visual images of own or others' body images: in some studies, the images are presented unaltered, while in others they are altered to appear longer or smaller. Altered activation of numerous brain structures has been reported, again focusing on emotion-processing regions. As research in this area progresses, this work has been transitioning from examining a single region of interest toward an approach that conceives of functioning neurocircuitries in the brain as the appropriate level of analysis (53).

12.1.2.5. Genetics

Family, twin, and molecular genetic studies are demonstrating a substantial role for genetic factors in the development of the eating disorders. There is uncertainty about the size of the genetic versus environmental contributions, both for AN and BN, although such studies commonly find genetic factors account for 40–60% of susceptibility to the illness (54). Increasingly, risk for ED is conceived of as reflecting a gene–environment interaction (55).

Increased rates of eating disorders among female family members of anorectic patients have been reported in several large series (56–58). For example, Theander (58) found a morbidity risk of AN among sisters of AN probands to be 6.6%. There is evidence of cross-transmission between the eating disorders, suggesting a shared familial liability (59). Klump et al. (60) found the lifetime risk of AN or BN among female relatives of an individual with an eating disorder to be 7–20 times that of the general population. Families with eating disorders also have increased rates of other psychiatric disorders including depression, anxiety, and obsessive-compulsive disorder. However, the vulnerabilities for depression and anxiety appear to be transmitted independently of the vulnerability for eating disorders, while obsessive-compulsive personality traits, like the vulnerability for eating disorders, appear to be a shared familial vulnerability (57).

Twin studies help to clarify the contribution of genetics to the familiality of eating disorder. Clinic-based samples indicate the concordance rate for AN is about 55% in MZ twins and 5% in DZ twins, whereas for BN it is 35% in MZ twins and 30% in DZ twins (59). While this suggests a significant heritability for AN but not for BN, population-based studies have also shown a significant heritability for BN as well (61, 62). Although it is estimated that greater than 50% of the variance in the occurrence of AN can be accounted for by genetic factors, twin studies suggest that 17–46% of the variance in both AN and BN is accounted for by non-shared environmental factors (63). Initial data indicate that differential paternal relationships, body weight teasing, peer group experiences, and life events may account for the development of eating pathology in one sibling versus another (63). More data are available for bulimia than for AN.

A wide variety of molecular genetic studies have been completed or are underway to identify underlying genes and loci. This work has focused in part on genes in neurotransmitter systems implicated in eating disorders (for example, serotonin or dopamine systems) (64). Symptoms thought to influence food intake have also been examined. This work has now migrated in the direction of genome-wide association studies, which may lead to the identification of a wider variety of genes (65). Such studies are challenging to conduct due to large sample size requirements but may be quite useful for identifying targets for future research.

12.2. Comorbidity

It has been hypothesized that eating disorders represent atypical affective disorders occurring in adolescent females at a time in their lives when body image issues are important. There are some findings supporting this view. Major depression, with about 45–68% meeting diagnostic criteria, is the most common comorbid disorder in both AN and BN (66–69). There is some evidence that women with the BN subtype of AN have more affective disorders than those with the restrictor subtype of anorexia (70). Symptoms of depression often predate the onset of the eating disorder, and follow-up of anorectics suggests an increased risk for affective disorder (69, 71). Controlled family studies have shown an increased incidence of primary affective disorder in the families of anorectics compared with families of controls (56, 69, 72). Biologic markers associated with primary affective disorders, such as elevated plasma cortisol levels, dexamethasone nonsuppression, low urine 3-methoxy-4-hydroxyphenylglycol levels, impaired growth hormone response to provocative stimuli, and an abnormal thyroid-stimulating hormone (TSH) response to thyrotropin-releasing hormone (TRH), also are found in anorectics, although the abnormalities appear reversible with weight gain. Semi-starvation can certainly contribute to depression (73), and there is evidence that starvation can lead to elevations in corticotropin-releasing hormone (CHF), which can contribute to depression (74).

A relationship between bipolar disorder and eating disorders has been suggested. Studies evaluated bipolar disorder in the relatives of eating disorder probands. Two studies found significantly higher rates of bipolar disorder in the relatives of anorectics than controls, and one study found higher rates of bipolar in relatives of BN than controls. Three controlled family interview studies have found depressive disorders, but not bipolar disorders, in the relatives of eating disorder probands. Numerous studies have now examined eating disorders among individuals with bipolar disorder and these studies have found elevated rates of ED, with binge eating disorders (BED) being most prominent in a number of these samples. This issue deserves further

attention, since phenomenologically, eating dysregulation, mood dysregulation, impulsivity and compulsivity, and exercise and activity, show some commonality between bipolar and eating disorders (75).

Newer evidence suggests that both AN and BN are related to anxiety disorders, including obsessive-compulsive disorders, and that anxiety is central in both the etiology and maintenance of eating disorders. During the acute illness, anorectics suffer from obsessions about food, weight, and body image, and they often have compulsions concerning dieting, exercising, food preparation, and weighing. There is evidence that caloric deprivation has a role in causing obsessional symptoms (73), and caloric deprivation may create an environment which allows the exacerbation of obsessional tendencies. A 10-year follow-up study indicated that 65% of anorectics had lifetime diagnosis of an anxiety disorder, with 34% having social phobia, 15% with agoraphobia, and 26% with obsessive-compulsive disorder (OCD) even excluding obsessions and compulsions concerning the eating disorder symptoms (69). In BN patients, although one study resulted in a lifetime diagnosis of OCD in 32% (76), other studies find a lower rate of OCD in BN patients compared to anorectics (77). In one recent study, 2/3 of both types of eating disorders had one or more lifetime anxiety disorder diagnosis, with OCD occurring in 41% and social phobia in 20%. The majority reported the onset of the anxiety disorders in childhood, before the onset of the eating disorder, thus pointing to a vulnerability factor for the development of the eating disorder. Also, subjects who had a history of eating disorder but were not currently ill with it still showed evidence for high anxiety (78). Recent imaging studies indicate that in anorectics compared to controls, there is evidence of greater activation of the limbic and paralimbic fear network when confronted with food and body image stimuli (79, 80).

The relationship between eating disorders and substance abuse has received considerable attention. The available data supports a relationship between the BN behaviors of binge-eating and purging and substance abuse, whether this is in an individual with BN or in the binge/purge subtype of AN (81). Substance abuse is not common in the restricter subtype of AN. Roughly 22% of BN patients report high alcohol intake, and 28% report a history of other drug abuse (82). There is also a high frequency of eating disorders in women who present for treatment of substance abuse. In a study of 61 adolescent females with a substance abuse problem, 28% had a diagnosable eating disorder (83). One possible reason for the association of eating disorders and substance abuse is that food deprivation increases the likelihood of substance abuse (84). However, this does not explain why there is so little substance abuse in restricter AN, who show even more food deprivation than the BN patients, and why there is more substance abuse in the binge/purge anorectic subtype than the restricter AN subtype. Another possible explanation for the relationship between eating disorders and substance abuse is through mediating factors, including personality factors, in eating disorders. There is evidence that women who have eating disorders but no substance abuse have fewer Cluster B personality disorders than women with substance abuse (85).

A "multi-impulsive" syndrome has been described in some patients with BN (82), which is characterized by heavy drinking and other drug abuse, stealing, suicide attempts, and self-injurious behavior (cutting). It may be that this form is a variant of borderline personality disorders (BPD). Several studies have found a strong relationship between BN and axis II disorders, particularly Cluster B or BPD (86, 87). In the study by Herzog et al., 27% of an outpatient sample of 210 females with eating disorders were diagnosed with personality disorders and the most common personality disorder was BPD (9%); none of the restricting AN patients had this diagnosis, but 8% of the BN patients and 12% of the binge/purge subtype of AN had this diagnosis.

In contrast to the high prevalence of Cluster B personality disorders in those eating disorders with binge/purge behavior, Cluster C personality disorders are most frequently observed in those with restricting AN. In one study of eating disorder patients, 35% of those with restricting AN met criteria for obsessive-compulsive personality disorder (OCPD), compared to 5% of those with BN (77), and in another study of adolescent females, those with AN had higher rates of OCPD compared to the normal controls (88). Cluster C changes may in part be related to starvation. Changes consistent with OCPD have been described in men undergoing semi-starvation, without these characteristics being present before the semi-starvation period (73). However, in a 6-year follow-up study of patients with a history of AN who no longer met diagnostic criteria for AN and who no longer were malnourished, Cluster C personality traits were still present, compared to a control group (88).

12.3. Epidemiology

AN historically has seemed an uncommon illness. In 1973, three separate psychiatric case registers in Scotland, England, and northeastern United States supported a low annual incidence of about 1 case per 100,000 population (89). Evidence suggests that the incidence of AN has increased. One study indicates that the incidence nearly doubled from 1960 to 1976 (90). Another study, which identified all anorectics in one Midwestern community between 1935 and 1984, indicated that the incidence has increased among females 15–24 years of age but not among older women or among males. The overall age-adjusted incidence rate per 100,000 person-years was 14.6 for females (91).

Prevalence studies indicate AN to be a common disorder in the age group at risk: 12–30 years of age. In 1976, Crisp et al. surveyed nine populations of high school girls in England. The prevalence was one severe case in 200 girls, and in those age 16 or older, the prevalence was even higher—one severe case in every 100 girls. In the Midwestern community study described above, the prevalence also was 1 case per 200 girls 15–19 years of age. Crisp et al. (92) and other authors have reported AN to be more prevalent in the higher socioeconomic classes, but no controlled studies support this hypothesis.

AN occurs predominantly in females, though the gender imbalance in AN may be less prominent than once thought. Historically, it was thought that only 4–10% of cases are males (91, 93), but recent evidence from the National Comorbidity Survey (94) finds a female to male ratio of 3:1, not 10:1. Clinically, except for amenorrhea, male anorectics are remarkably similar to the females. AN appears to be uncommon in poorly developed countries, and it is infrequent among blacks in the United States. It is overrepresented in females in certain occupations, such as models and ballerinas, who must rigorously control their body shape (4, 13).

BN is more common than AN with the lifetime prevalence estimated to be 1–3% of females in the United States. Most research studies of prevalence have been done in college and high school females, but it is unclear what the prevalence rate is in the general population. As with AN, BN has been thought to occur predominantly in females, with only about 10% of cases being males, but NCS-R data suggest that, in community samples, about 25% of those with BN are male. BN typically develops a bit later than AN, in later adolescence or early adulthood. Like AN, BN is more common in western cultures where food is abundant and slimness is highly valued. There is evidence that BN increased and is more prevalent in those who were born after 1960 (95). Dieting typically precedes the onset of BN symptoms, although there are cases where binge-eating precedes dieting (96).

12.4. Clinical Picture

12.4.1. AN

The essential clinical features of AN and a comparison with the features of BN are listed in Table 12.1. AN typically begins with a simple diet adopted in response to concern about real or imagined overweight. At first, high-calorie foods are eliminated. Then other foods are systematically curtailed as negative attitude toward food develops. As weight loss progresses, disgust about eating and intense fear about being obese begin to outweigh hunger. The term “anorexia” is a misnomer because true loss of appetite is uncommon until late in the illness. Weight loss progresses until the patient becomes emaciated. The anorectic is typically unaware of her extreme thinness; instead, she continues to feel fat and loses more weight.

Attempts to assess body image disturbance, or the anorectic’s failure to recognize her starved body as being too thin or to regard herself as normal, or even overweight, in the face of increasing cachexia, have relied on visual size estimation devices. Using these devices, various investigators have confirmed that anorectics overestimate the width of body parts, but there are wide individual variations among anorectics in their body size estimates (97, 98). Compared with anorectics who more accurately estimate the size of body parts, those who are relatively inaccurate have been found to be more likely to fail to acknowledge their illness, to vomit, to be more severely malnourished, to gain less weight during treatment, and to have failed to gain weight during previous hospitalizations (97, 99). Although body size overestimation is significant in a subgroup of AN, it cannot be considered unique to this population, since some studies have found no significant mean differences between anorectics and control groups (97, 99).

Anorectics exhibit odd behavior around food. They hide food all over the house. During mealtimes they deviously dispose of food. They cut food into tiny pieces or spend much time arranging food on their plates. Confrontation about these behaviors is often met with denial. Yet anorectics think constantly about food, often collect recipes, and engage in elaborate food preparation for others. Approximately 50% begin to gorge themselves with food (binge eat), up to 40% induce vomiting, and may begin using laxatives and diuretics in an attempt to reduce weight (100, 101). They also may become hyperactive and engage in strenuous ritualistic exercises to control weight.

Attempts to delineate subgroups have focused on clinical differences between anorectics who binge eat and those who do not. In two large surveys, BN anorectic patients were characterized by self-induced vomiting and by abuse of laxatives and diuretics (100, 101). They displayed impulsive behaviors, e.g., alcohol abuse, stealing, and suicide attempts. They were more extroverted but manifested greater anxiety, guilt, depression, and interpersonal sensitivity and had more somatic complaints than did anorectics who exclusively dieted to lose weight. In one study, a high frequency of obesity was found in mothers of the BN anorectics (101). The delineation of these subgroups extends to the families. The incidence of alcoholism and drug abuse disorders is higher in families of BN anorectics than in families of non-BN anorectics (102, 103). The BN subgroup of AN remarkably shares characteristics with BN. Possibly these two populations form a single group within the eating disorders. Anorexia Nervosa patients who purge but who do not objectively binge-eat also are encountered.

12.4.2. BN

The main feature that distinguishes BN from AN is that early attempts to restrict food intake leads to episodes of binge-eating, defined as rapid consumption of large amounts of food, usually while alone, with a sense of loss of control. Typically individuals with BN restrict their food early in the day. Binges are typically in the afternoon or evening, and although the amount eaten

in a binge varies, patients may eat 5,000 or more calories in a few hours (104). Subjects with BN can usually identify safe foods which do not result in a binge, and unsafe or "forbidden" foods which result in a binge (usually high-calorie carbohydrate or fat foods). This was demonstrated in a study which found that subjects with BN reported a greater urge to binge and higher levels of stress and physiological arousal when confronted with favorite binge foods compared with a control group (105). Binge-eating is usually followed by self-induced vomiting, although other purging compensatory mechanisms, including misuse of large amounts of laxatives or diuretics, follows. Although people with BN at first feel they can control their eating binges, over time there is an increase in binge frequency and duration. There is a small subgroup who do not purge. Body weight in BN is typically in the normal weight range.

As in AN, a subgroup of bulimia has been identified with diffuse difficulties in controlling impulses; this "multi-impulsive" group may abuse alcohol or drugs, may steal compulsively, and may engage in frequent self-injurious behavior such as cutting (82).

12.5. Clinical Course

12.5.1. AN

Onset of AN occurs from prepuberty to young adulthood, generally between the ages 10 and 30. Most commonly, the disorder begins between the ages of 13 and 20, and the mean age of onset is 16 (58, 106). Although rare cases outside this range are described, they must be scrutinized to rule out other psychiatric or organic disorders simulating AN. Some investigators find no distinct premorbid personality, whereas others describe a typical case as well behaved, perfectionistic, obsessional, introverted, and shy. Onset of dieting has been associated with precipitating events, such as moving to a new school, or a traumatic event involving dating or peer relations, but often, no specific reason is apparent.

AN has a variable course and outcome. The course varies from spontaneous recovery without treatment to gradual or rapid deterioration, resulting in death. There may be lasting recovery after an episode of weight loss or a fluctuating pattern of illness marked by remission and exacerbations over many years. Although the short-term response of anorectics to well-organized hospital treatment programs is good, there are no consistent data concerning the effect of treatment on long-term outcome.

No follow-up study done has been free of methodological problems involving, primarily, sampling biases, inconsistent follow-up intervals, and different outcome measurement (58, 71, 107–110). Reviews of studies with similar longer term follow-up periods indicate the following (111, 112). Overall, about 50% fully recover over time, about 30% do fairly well but continue to have significant eating disorder symptoms as well as problems with social, sexual, and psychological adjustment, and about 20% do poorly. A significant number remain amenorrheic despite a return to normal weight. Body weight remains persistently below 75% of normal in up to 25%. Obesity develops in less than 8%. Although weight may be normal at follow-up, abnormal eating behavior may persist; one-half still practice dietary restriction and avoid high-calorie foods, and binge-eating or compulsive overeating, vomiting, and laxative abuse are common, and many meet the criteria for BN at follow-up. Thus, there is a fair amount of crossover from AN to BN. Up to half the anorectics have unipolar affective disorder at follow-up (69, 71). Other common psychiatric problems at follow-up are obsessive-compulsive symptoms, social phobias, drug dependency, and stealing. Several studies indicate that psychiatric symptoms are more common and severe in anorectics who at follow-up have low weight and abnormal eating behavior or are preoccupied with food and weight (69).

The most consistent favorable prognostic feature is early age of onset, and the most consistent unfavorable ones are late age of onset and more previous hospitalizations (58, 113). Poorer outcome also has been associated with greater length of illness, the presence of bulimia, vomiting and laxative abuse, overestimation of body size, disturbed family relationships, more physical complaints, and symptoms of neuroticism, depression and obsessionality. Recently, lower weight at hospital discharge has been found to be a predicter of relapse (114).

Anorexia Nervosa carries a considerable mortality, with a standardized mortality ratio up to 12.82 (108). The usual causes of death are starvation and electrolyte disturbance, but suicide is also a significant contributor. Although most studies report a death rate of less than 8%, several report a rate greater than 15%. Longer term studies tend to show higher mortality rates (113, 115–117). The most notable of these, a Scandinavian study conducted over 22 years, found an 18% mortality (116). The suicide rate was 5%. Most studies report suicide rates of around 1%. A recent meta-analysis of 36 mortality studies finds a standardized mortality rate in AN of 5.86 (118) likely due to the establishment of specialized care units (119).

12.5.2. BN

The mean age of onset of BN is a bit later than AN, with mean age of onset of binge-eating of 18 years (120). The onset of vomiting is on average 1 year later. Premorbid characteristics are similar as for AN, except, unlike the restricter anorectics, in many there are generalized impulse-control problems. The typical individual with BN is symptomatic for 3–6 years before seeking treatment, and the frequency of the BN behaviors generally increases over time (120).

Less is known about the course of BN than about AN, but it is clear that BN has a relapsing course. Multiple treatment studies indicate significant improvement over the short term, but in the longer term relapses are frequent, both with treatment and in naturalistic studies (121). There is very little crossover to AN. A recent meta-analysis of mortality rates in BN found them to be modestly elevated [SMR = 1.93; (120)]. Most of the follow-up reports of treatment studies indicate that about 50% had recovered at a follow-up interval of 5 years or more, while 20% continue to meet full criteria for BN, and 30% had experienced relapse into BN symptoms. One recent review of the follow-up studies for bulimia (122) indicates that there is no stable recovery for the first 5–6 years after intake into a BN study, but there is a general tendency for increase of recovery with increasing length of follow-up, so that after about 10 years about 70% show at least partial recovery. However, as many as 25% may still have BN symptoms, indicating a high rate of chronicity.

Several prognostic indicators for BN have been identified (122). There is general agreement that a high degree of severity of BN symptoms, particularly vomiting, predicts a worse outcome, while a short duration of illness predicts a better outcome. Substance abuse seems to predict a worse outcome. Borderline personality disorder and Cluster B personality disorders predict a worse outcome, perhaps related to the issue of multi-impulsivity, which is present in many people with BN and which also predicts a worse outcome.

12.6. Medical Findings

Medical abnormalities and complications noted in AN and a comparison with those noted in BN are given in Table 12.2. Physical and medical abnormalities in AN are largely secondary to the compromised nutritional state and disturbed eating habits, and most of these resolve with restoration of sound eating behaviors, sound nutrition and return to normal weight, with the possible exception of reduced bone density, which does not recover (123). Prolonged amenorrhea with low weight is associated with potentially irreversible osteopenia and an increased rate of pathologic fractures (124). Prepubertal patients may experience growth arrest and may not grow to anticipated heights. Amenorrhea is invariably present and may begin before, concurrently with, or after the onset of dieting (125). Some patients do not regain their menses with weight gain, suggesting that other factors than body weight influence this process. One of these factors may be a finding in anorectics at low weight of an "immaturity" in the pattern of 1uteinizing hormone (LH) functioning, resembling that of prepubertal girls. After weight gain, the LH pattern usually returns to normal, but some anorectics continue to have an immature pattern. In one study those patients who continued to have abnormal eating patterns also continued to have an immature LH secretory pattern (126). There are some other abnormalities which are not clearly resolved with weight gain. For example, abnormal CT scans of the brain may be found in more than half of anorectic patients (127) and there is evidence lacking that this always resolves with weight gain. Common physical findings in AN are hypotension, hypothermia, bradycardia, dry skin, and lanugo. Less common features include hair loss, petechiae, peripheral edema, and carotenemic skin.

BN patients are less medically compromised (128, 129). Their most common problem is fluid and electrolyte abnormalities, which are found in about 50%, secondary to variable combinations of vomiting, laxative, and diuretic abuse. The most common picture is one of alkalosis manifested by elevated serum bicarbonate, sometimes accompanied by hypokalemia and hypochloremia. These fluid and electrolyte abnormalities are found in a more severe form in the BN subtype of AN. People with BN may be intermittently amenorrheic. Salivary gland swelling, typically of the parotid glands is common. The etiology of this is somewhat unclear, but likely related to vomiting, and mildly elevated salivary amylase changes are likely associated. BN patients often also have dentition problems, particularly erosion of the surface dental enamel on the back of the teeth where the highly acid contents project due to vomiting (130). Rare but dangerous complications include gastric rupture or esophageal tear.

12.7. Differential Diagnosis

The major confounding diagnosis is BN. The unclear boundaries between AN and BN are indicated by the fact that one frequently develops from the other and by the overlap in their essential features (see Table 12.1). Although binge-eating occurs in both BN and AN, BN patients generally maintain weight within a normal range and do not show extreme pursuit of thinness. Body image disturbance has not yet been systematically assessed in BN.

AN must be differentiated from peculiar eating behaviors and weight loss which can occur in several other disorders. In general, the differentiation can readily be made on the basis of positive criteria of AN, such as fear of becoming obese and pursuit of thinness, which are absent in the other disorders. For example, weight loss is common in depressive disorders but is generally more severe in AN. Whereas depressed patients are aware of a loss of appetite, anorectics generally have a normal appetite, which they may deny. Anorectics, in contrast to depressives, are preoccupied with food. Agitation can be seen in depressive disorders, but it differs from the ritualistic activity of an anorectic. Weight loss and peculiar eating behavior are also

TABLE 12.2. Major medical abnormalities of AN and BN.

	AN	BN
Hematologic	Leukopenia	
	Thrombocytopenia	
	Bone marrow hypocellularity	
	Low ESR	
Renal	Elevated BUN (dehydration)	Elevated BUN (dehydration)
	Decreased GFR	
	Partial diabetes insipidus	
Metabolism	Hypercholesterolemia	
	High carotene	
	Low plasma zinc	
Gastrointestinal	Delayed gastric emptying	Altered gastric emptying
	Low gastric secretion	Salivary gland swelling
	Abnormal liver function results	Elevated amylase
	Superior mesenteric artery syndrome	Pancreatitis
	Pancreatitis	
Cardiovascular	EKG abnormalities:	Cardiomyopathy in ipecac abusers
	Arrythmias, QT prolongation, bradycardia	Hypokalemic-related ST changes,
	Altered circulatory dynamics	QT prolongation in EKG
	Hypotension	
	Edema	
	Congestive heart failure with refeeding	
Dental	Dental caries	Dental caries
	Enamel erosion	Enamel erosion
Skeletal	Demineralization,	
	Stress fractures	
	Delayed bone age	
Fluid and Electrolyte	Dehydration	Dehydration
	Alkalosis	Alkalosis
	Hypochloremia	Hypochloremia
	Hypokalemia	Hypokalemia
C.N.S.	Nonspecific E.E.G. abnormalities	Nonspecific E.E.G abnormalities
	CT/MRI: enlarged ventricles,	CT/fMRI: decreased cerebral blood flow changes
	Decreased gray and white matter	
	Changes in blood flow	
Gonadal Steroids	Low LH, FSH	May be hypoestrogenemic
	Impaired response to LHRH	
	Immature LH pattern	
	Low urinary gonadotropins	
	Low urinary estrogens	
	Abnormal estrogen metabolism	
Thyroid	Low T3, high rT3	Impaired TRH responsiveness
	Impaired TRH responsiveness	
Growth Hormone	Elevated basal GH	Pathological responsiveness to provocative stimuli
	Pathological responsiveness to provocative stimuli	
Prolactin	Pathological responsiveness to provocative stimuli	Elevated basal prolactin
Glucose	Abnormal glucose tolerance test	
	Fasting hypoglycemia	
Adrenal	Elevated cortisol	Dexamethasone test positive
	Change in cortisol metabolism and secretion	
	Dexamethasone test positive	

sometimes seen in schizophrenics, usually on the basis of delusions. However, the delusions of schizophrenics differ in content and are not concerned with caloric content or fear of weight gain.

It is important to ascertain medical conditions that accompany or simulate AN. Lesions of the pituitary or the hypothalamus may be accompanied by appetite disturbance and weight loss. Starvation results in some of the symptoms found in AN and BN. One important study, the Minnesota Semi-starvation Experiment (73), demonstrated that like eating disorder patients, the healthy male conscientious objectors who were subjected to semi-starvation quickly developed an intense preoccupation with food and eating, mood changes, diminished social interest, and after several weeks even a tendency to binge-eating, However, in general, starvation, resulting from causes other than AN, is associated with inactivity and apathy and not with the intense fear

of weight gain, body image distortion, alertness, and hyperactivity seen in anorectics (131). In a recent follow-up study of 19 of the original 36 conscientious objectors who participated in the Minnesota Semi-starvation Experiment, subjects described tiredness and apathy, and none recalled feelings of alertness or hyperactivity during the semi-starvation (132).

The differential diagnosis of BN includes a variety of organic syndromes which result in hyperphagia (Prader–Willi, Klüver–Bucy, Kleine–Levine). However, these patients do not show the typical episodes of binge-eating. Rather, they display a near constant hyperphagia.

BN must be differentiated from binge-eating disorder. These patients have the episodic pattern of binge-eating like the BN, but they do not show the inappropriate compensatory behavior characteristic of BN (e.g., purging, fasting, excess exercise). Also, individuals with binge-eating disorder are almost all overweight, in contrast to BN, who are generally in the normal weight range.

12.8. Treatment

12.8.1. AN

AN remains a serious disorder remarkably resistant to a wide range of interventions. To date, no psychological or pharmacological intervention has been identified which dramatically and reliably alters the dysfunctional thinking and associated behaviors which accompany it in adults, although family-based therapy shows considerable promise in adolescents. Overall, few controlled treatment trials have examined the treatments for AN. Since there are multiple causative factors and multiple deficiencies in psychological, social, behavioral, and physical functioning, the treatment program must be multidimensional and flexible. There is no agreement about the best treatment for adults. Treatment currently involves a combination of medical management, nutritional education and rehabilitation often using behavioral techniques, re-educative personal therapy to change core dysfunctional cognitions and attitudes, family therapy, and, sometimes, pharmacotherapy.

The immediate aim of treatment during the acute anorectic phase is to correct dehydration and electrolyte imbalance and restore the nutritional state to normal. Starvation itself can lead to many problems, including depression, sleep disturbance, preoccupation with food, and irritability, and improvement in the patient's psychological state will occur with nutritional rehabilitation (133, 134). Treatment during the acute state is done most efficiently in a structured hospital treatment program, and also in specialized partial hospital programs. It is advisable to prescribe a structured diet gradually increasing calories to avoid stomach dilatation and circulation overload. Close observation during and after meals will minimize surreptitious mealtime behavior, such as hiding food and vomiting. Behavioral contingencies after an operant conditioning paradigm probably increase the rate of weight gain (135). However, a randomized controlled treatment study did not demonstrate a clear advantage, expressed as weight gain, for behavior therapy (136). Because many anorectic patients do not acknowledge that a problem exists, it is essential to obtain the family's support so that firm treatments can be effected.

Those patients who are less severely ill, are not vomiting or using laxatives, are motivated to adhere to treatment, and have family that will cooperate with prescribed treatment may respond to outpatient treatment, but they should be carefully monitored and referred to more intensive settings such as inpatient or partial hospital care if no progress or deterioration occurs over several weeks.

Counseling of family members is a necessary component of an effective treatment program. This involves educating the family about the disorder, assessing the family's impact on maintaining the order, and assisting in methods to promote normal functioning of the patient.

Evidence suggests that a specific type of structured family therapy, typically referred to as family-based therapy (FBT), which first addresses the specific eating issues followed by psychological issues is helpful for adolescents with AN who still reside at home (137–140).

Psychotherapy is typically a regular part of treatment. Individual psychotherapy should aim at correcting cognitive errors of thinking, promoting independence, accepting responsibilities, improving psychosocial skill deficits, and promoting a positive self-concept.

However, the few studies that have been done do not clearly demonstrate superiority of any specific therapy. The specific therapies that have been studied include cognitive behavior therapy, cognitive psychoanalytic and educational behavioral therapy, dietary counseling, individual supportive therapy and family therapy (141–146). Although cognitive behavior therapy has shown to have some effectiveness (144), interpersonal psychotherapy has also received attention (147). A recent controlled outpatient study comparing cognitive behavioral, interpersonal and a control treatment of nonspecific supportive clinical management (involving education, nutritional advice and supportive therapy), found the nonspecific supportive clinical management to be superior to the two specialized therapies, while the cognitive behavioral and interpersonal therapies did not differ significantly from each other (148).

Recent reports have described a revised form of Cognitive Behavior Therapy (CBT-E) for adults and adolescents with AN (149, 150). There is as yet no proven pharmacological treatment for AN. A major problem may be due to the neurochemical effect of starvation. Although a variety of medications including antidepressants, classical antipsychotics, atypical antipsychotics, lithium, and antihistamines have been studied in the treatment of low weight anorectics, primarily focusing on their ability to promote weight gain and improve symptoms, no drug has proven to be of clinical value (151–158). Another approach is to utilize medications after weight recovery and evaluate their effectiveness on weight maintenance and improvements in comorbid psychopathology. One placebo-controlled study indicated that fluoxetine benefited non-BN weight recovered anorectics in prevention of relapse after 1 year (159). However, a recent well designed, randomized, double-blind placebo-controlled study of fluoxetine in weight recovered anorectics treated for 1 year failed to demonstrate a benefit from fluoxetine in the prevention of relapse (160). All patients in this study received cognitive behavior therapy. There was no difference in results in the restricter versus BN subgroups.

Recent work has examined atypical antipsychotics for AN. Results have been mixed, with some studies suggesting benefits (155, 156) as it appears that patient concern about weight gain with these agents is prominent (161). Despite the generally negative results in controlled studies, many clinicians utilize a variety of medications in an attempt to treat the associated comorbidities of depression, anxiety, and obsessive-compulsive problems, more often during the weight recovered phase than the acute low weight phase. The most frequently used medications are the SSRIs to treat depression and obsessive-compulsive symptoms, but low dose atypical antipsychotics are also utilized, as well as antianxiety agents. More studies of the antipsychotics, antidepressants, and newly developing agents are sorely needed. Such pilot studies should probably target potential symptom maintenance mechanisms, rather than global AN outcome (162).

12.8.2. BN

In contrast to anorectics, most patients with BN can be successfully treated with outpatient care and inpatient care is rarely indicated. More than 40 randomized controlled trials have been done to assess treatment efficacy of medications (primarily antidepressants), medication plus therapy, and therapies alone (163, 164). Many antidepressants have been demonstrated to be effective in significantly reducing the BN symptoms in the short term, and there is a definite anti-binge effect separate from the effect on mood (42, 158). Fluoxetine is the only medication that has been approved by the US Food and Drug Administration in the treatment of BN, and in the supporting controlled study, a higher dose of 60 mg was found to be the most effective, which is higher than the typical dose to treat depression (165). The difficulty is that the positive effect of the antidepressants is not sustained, and that relapses occur despite continued treatment with medications (158).

A novel pharmacological approach to the treatment of bulimia, targeting the peripheral nervous system, was reported by Faris et al (24). The group hypothesized that increase in vagal nerve activity resulted from repeated cycles of binge-purge episodes, which led to increased urges to maintain the binge-purge behavior. They chose ondansetron, an inhibitor of the $5HT_3$ receptors primarily in the vagal afferents, in an attempt to correct the vagal hyperactivity. In a randomized double-blind placebo-controlled 4-week treatment study of severe BN, there was a 50% decrease in binge-purge episodes, a 50% decrease in time spent in binge-purge activity and a 33% increase in the number of meals not followed by purging. This interesting hypothesis requires further study.

Cognitive behavior therapy (CBT), either in a group setting or individual format, which focuses on restructuring the maladaptive behaviors plus the associated thinking which supports and maintains the disorder, has been repeatedly shown to be the most effective treatment for bulimia, even when compared to antidepressants (166–168). Results indicate about one-half of patients recover during the usual 4–6 months of treatment. An enhanced version of CBT (CBT-E) has been developed and appears to be effective for bulimic symptoms (169). Of note, a recent trial compared CBT-E given for 20 sessions to 2 years of weekly psychoanalytic psychotherapy (170). Despite the large difference in trearment dose, CBT-E was more effective than psychoanalytic psychotherapy. Another short-term therapy, interpersonal psychotherapy, has been studied and found to be comparable in efficacy to CBT for bulimia, except that it appears to take longer to get similar results (171). For adolescents, there is evidence that Family-Based Therapy may be effective (172).

Studies have also been done investigating the combination of psychotherapy, usually CBT, and antidepressants (166–168, 173). In general, CBT is more effective than antidepressants, and the combination of antidepressants and CBT is more effective than antidepressants alone. Although BN symptoms do not appear to be improved with the combination of antidepressants and CBT over CBT alone, there is evidence that depression, anxiety, and possibly dietary restriction improve with the combination (168).

Although the treatment of choice for BN is psychotherapy, many clinicians begin with an SSRI like fluoxetine or sertraline because specialized therapies may not be available. This is initially helpful to many, particularly if there are substantial concurrent symptoms of depression, anxiety, or obsessions. Further, these medications are often helpful to those who have had a suboptimal response to psychotherapy. Some clinicians favor starting antidepressants along with CBT. It is important to remember that despite initial success with treatment, relapses later on are common.

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13
Antisocial Personality Disorder

Karen J. Derefinko, Ph.D. and Thomas A. Widiger, Ph.D.

Abstract The present chapter discusses the medical understanding of antisocial personality disorder (APSD), including research concerning its etiology, prevalence, pathology, differential diagnosis, and treatment. ASPD, and the closely related diagnosis of psychopathy, appear to be products of a strong genetic disposition interacting with a variety of environmental contributions. Epidemiological studies indicate that ASPD and psychopathy are much more prevalent in men than in women, a finding that is supported by general personality research. Theories of pathology are numerous, but generally point to several distinct deficits; psychopathy has been associated empirically with abnormal affective processing, neuroanatomical abnormalities, psychophysiological arousal system impairments, deficits in cognitive functioning, and maladaptive personality constellations. While considered diagnostically reliable, ASPD and psychopathy are highly comorbid with substance dependence and narcissistic personality disorder due to similar criteria, making differential diagnosis difficult. Finally, treatment for psychopathy and ASPD remains a very controversial subject; while meta-analytic findings demonstrate positive results, considerable evidence also indicates that these disorders are resistant to typical interventions.

Keywords Antisocial • Psychopathy • Personality disorders • Pathology • Dimensional models

13.1. Definition

The Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) (1) defined antisocial personality disorder (ASPD) as a pervasive pattern of disregard for and violation of the rights of others. DSM-IV has been supplanted by the fifth edition of this diagnostic manual [DSM-5; (2)]. However, no changes were made to the personality disorders section. Therefore, all references to DSM-IV apply as well to DSM-5. DSM-5 does include within Section 3, for emerging models and measures, a reference to a dimensional trait model conceptualization of the personality disorders. This conceptualization is also included herein.

The primary diagnostic criteria for ASPD include criminal activity, deceitfulness, impulsivity, aggression, recklessness, irresponsibility, and indifference to the mistreatment of others. The DSM-IV conceptualization of ASPD was based substantially on the features of psychopathy originally outlined by Cleckley (3, 4). In fact, the text of the DSM-IV indicated that psychopathy is another term for the disorder (1). However, some have argued that the constructs of ASPD and psychopathy are not interchangeable due to the failure of DSM ASPD to include the breadth of Cleckley's psychopathy traits (5, 6). In support, the most widely recognized psychopathy measure, the Psychopathy Checklist-Revised (PCL-R) (7, 8), includes a few traits not found in the DSM-IV definition of ASPD: Glib charm, lack of empathy, shallow affect, and arrogance. Additionally, Cleckley identified other psychopathy traits not present in either the DSM-IV or the PCL-R criterion sets, notably the "absence of 'nervousness'" (3) (p. 206), which some suggest is a fundamental trait of psychopathy (9).

K.J. Derefinko, Ph.D. (✉)
Postdoctoral Fellow, Department of Psychology, University of Kentucky, Lexington, KY, USA
e-mail: kjdere2@uky.edu

T.A. Widiger, Ph.D.
Professor, Department of Psychology, University of Kentucky, Lexington, KY, USA
e-mail: widiger@email.uky.edu

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TABLE 13.1 Domains and facets of the Five Factor Model (FFM).

Domains	Facets
Neuroticism (N)	N1: Anxiety
	N2: Angry hostility
	N3: Depression
	N4:Self-consciousness
	N5: Impulsiveness
	N6: Vulnerability
Extroversion (E)	E1: Warmth
	E2: Gregariousness
	E3: Assertiveness
	E4: Activity
	E5: Excitement seeking
	E6: Positive emotions
Openness to Experience (O)	O1: Fantasy
	O2: Aesthetics
	O3: Feelings
	O4: Actions
	O5: Ideas
	O6: Values
Agreeableness (A)	A1: Trust
	A2: Straightforwardness
	A3: Altruism
	A4: Compliance
	A5: Modesty
	A6: Tender-mindedness
Conscientiousness (C)	C1: Competence
	C2: Order
	C3: Dutifulness
	C4: Achievement striving
	C5: Self-discipline
	C6: Deliberation

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It is also helpful to understand ASPD from the perspective of general personality structure; more specifically, as a maladaptive variant of personality traits evident within the general population. Our preference is to use the five factor model of personality (FFM), the predominant dimensional model of general personality (10–12). The FFM includes five broad domains, each with six specific facets. The domains include neuroticism (N: anxiousness, angry hostility, trait depression, self-consciousness, impulsiveness, vulnerability), extroversion (E; warmth, gregariousness, assertiveness, activity, excitement seeking, positive emotions), openness to experience (O; fantasy, aesthetics, feelings, actions, ideas, values), agreeableness (A; trust, straightforwardness, altruism, compliance, modesty, tender mindedness), and conscientiousness (C; competence, order, dutifulness, achievement striving, self-discipline, deliberation). A complete list of the domains and facets of the FFM can be found in Table 13.1. The five domains of the FFM align with the five domains of the DSM-5 dimensional trait model (DSM-5 negative affectivity aligns with FFM neuroticism, DSM-5 detachment with introversion, DSM-5 antagonism with low agreeableness, DSM-5 disinhibition with low conscientiousness, and DSM-5 psychoticism with openness) (13).

Considerable research has been conducted using the five-factor model to understand psychopathy (14–17) and ASPD (17–20). Importantly, the five-factor model conceptualization articulates the similarities and differences between the psychopathy and ASPD constructs within a common framework. For instance, while both ASPD and psychopathy are represented by the A facets of low straightforwardness (deception), low altruism (exploitation), and low compliance (antagonistic aggression), psychopathy also includes the other A facets of low modesty (arrogance), low tender-mindedness (callousness), and low trust (suspiciousness). ASPD and psychopathy share several facets of C, including low dutifulness (irresponsible), low self-discipline (negligent), and low deliberation (rash). With regard to N, both ASPD and psychopathy are represented by high angry hostility and high impulsiveness. However, psychopathy is also characterized by the N facets of low self-

consciousness (glib), low anxiety (absence of nervousness), low depressiveness (self-contentment) and low vulnerability (fearless). In terms of E, both psychopathy and ASPD are represented by high excitement seeking (foolhardy), and high assertiveness (dominant), but the psychopath is also low in warmth (cold and distant). An advantage of conceptualizing psychopathy from the perspective of the FFM is that it allows for a clear distinction between the successful psychopath (who manages to avoid exposure or arrest) and the unsuccessful psychopath (21). The successful psychopath is characterized by the traits of high conscientiousness (self-discipline, achievement-striving, and competence), whereas, conversely, the unsuccessful psychopath by low traits of conscientiousness [rash, irresponsible, and negligent; (22)]. There is also now a published measure to assess psychopathy from the perspective of the FFM (23), which aligns well with the DSM-5 traits for ASPD (24), albeit the latter does not include traits involving low neuroticism (i.e., glib charm and fearlessness) or extroversion (e.g., dominance).

Thus, while ASPD and psychopathy appear to have substantial overlap, the pronounced differences with regard to aspects of personality indicate potentially meaningful divergence. This divergence is reflected in epidemiological and pathological differences across the two alternative conceptualizations. For this reason, these diagnoses will be discussed separately in the relevant sections. In addition, among the two conceptualizations, considerably more research has been conducted for psychopathy, particularly within the pathology domain. Again, while we do not want to use the disorders interchangeably, the weight of the psychopathy literature deserves consideration.

13.2. Etiology

There is considerable evidence of the heritability of antisocial behavior. In animal studies of temperament, selection studies (where brother-sister matings are carried out over many generations) have been successful in breeding rats for specific traits, including aggression, indicating that part of what is genetically transmitted is temperament (25, 26). In research with humans, the results of twin and adoption studies indicate a strong genetic component for antisocial behavior. Generally speaking, genetic factors are believed to account for approximately 50% of variation in antisocial behavior, although this estimate may be influenced by the interaction among genes, or between genes and environment (27, 28). However, when additive (interactive) and nonadditive (singular) genetic contributions are assessed, the genetic contribution remains resilient. Waldman and Rhee (29) provided results of a meta-analysis of 51 twin and adoption studies of antisocial behavior that indicated a substantial contribution of both additive genetic factors (*effect size* = .32) and nonadditive genetic factors (*effect size* = .09). These results indicate that specific, heritable genes may be important contributors to generalized antisocial behavior. Of interest, twin studies that have explored the development of antisocial behavior in children suggest that there may be differences in heritability of antisocial behavior dependent on the presence of psychopathic features. Viding and colleagues (30) found that the additive genetic heritability of antisocial behavior without traits of psychopathy is similar to prior estimates (30%) and the expression more heavily influenced by shared environmental factors, whereas antisocial behavior with traits of psychopathy is considerably more genetically-based (81%), with little or no influence of shared environment [see (31) for a review]. Other research has indicated that the stability of psychopathic traits is also primarily genetically-based (32), suggesting a chronic and refractory course. This may suggest that assessing for psychopathic traits may be of value when exploring the development of antisocial behavior, and this resilience to environment may be a factor in treatment development efforts for psychopathy.

Although no genes have been clearly identified as etiological precursors to ASPD or psychopathy, several candidates remain a focus of this research, including those that are thought to underlie the related predisposing disorder of attention-deficit/hyperactivity (ADHD), and those that are related to neurotransmitter systems relevant to aggressive and criminal behavior, such as the dopaminergic and serotonergic systems (29, 33, 34). In a 2006 review of this area, Minzenberg and Siever provided several genetic polymorphisms that are the focus of recent research in antisocial and aggressive behavior (33). Within the serotonergic system, alleles that are involved in the synthesis (*U* and *LL*), transportation (*s*), reception (*5HTR1B, 5HTR1A*), and metabolism (*MAO-A*) of neuronal serotonin have all been associated with anger, aggressive behavior, impulsivity, and antisociality, as have several receptor polymorphisms (*DRD2, DRD3, DRD4*) and genes related to metabolism (DBH) of the dopaminergic system, and catechol-O-methyltransferase (*COMT*), a polymorphism associated with the breakdown of dopamine and norepinephrine [see (33, 35) for a review]. A 2012 review of genetic contributions specific to psychopathy has implicated the valine allele of the COMT gene, the low activity allele of the MAOA gene (MAOA-L), and the short allele of the serotonin transporter linked polymorphic region gene (5-HTTLPRs) (36). However, as others have noted, this area of research is still very new and almost no replication of these findings has been achieved, suggesting that these preliminary findings are not yet considered conclusive evidence of any specific genetic contribution (31).

Numerous environmental factors have also been implicated in the etiology of antisocial behavior. Shared, or common, environmental influences account for 15% to 20% of variation in criminality or delinquency (28, 37). This finding is remarkably robust even when compared to other psychiatric disorders with known environmental components such as affective and substance use disorders (38), and indicates something distinct about the shared environmental influence on antisocial behavior.

The modeling or learning of aggressive behaviors is more likely to occur in environments that have higher incidents of this type of behavior, or that condone antisociality and violence (39). Not surprisingly, shared environmental factors such as low family income, inner city residence, poor parental supervision, single-parent households, rearing by antisocial parents, delinquent siblings, parental conflict, harsh discipline, neglect, large family size, young mother, and depressed mother have all been implicated as risk factors for antisocial behavior (40). The effects of these factors are not limited to learning, however. For instance, neglect and physical abuse can generate several possible courses to antisocial and aggressive behavior, such as desensitization to pain, impulsive coping styles, changes in self-esteem, and early contact with the justice system (41). Nonshared environmental influences are also substantial contributors. Factors specific to the individual appear to account for fully 30% of antisocial behavior variance (27). In short, this is the remaining variance not accounted for by genetic (50%) or shared environmental (20%) influences. Nonshared environmental factors may include delinquent peers, individual social and academic experiences, sexual abuse, or sustaining an injury not shared by siblings, such as a head injury.

Unfortunately, the interactive effects of genetic and environmental influences are difficult to tease apart, and likely create confusion about what these estimates mean in terms of causation. For example, the individual who is genetically predisposed to antisocial behavior will subsequently elicit environmental factors associated with criminal outcomes, such as peer problems, academic difficulty, and harsh discipline from parents. In addition, antisocial individuals receive their genes from antisocial parents who also exhibit delinquent and irresponsible behavior, thus creating an immediate home environment that is likely to model instability and criminality. Concerns surrounding the interaction of environmental and genetic factors have led to research designs that have focused more directly at making these distinctions. Studies that explicitly address this issue have found that environmental factors continue to play a large part in etiology of antisocial behavior beyond genetic factors alone. For instance, after controlling for the genetic component of physical maltreatment, Jaffee, Caspi, Moffitt, and Taylor (42) found that the environmental etiological effect of physical maltreatment remained.

In addition to genetic and environmental influences, other work has focused on the relative contribution of the interaction of genes and environment to the development of antisocial behavior. For example, Caspi and colleagues (34) found that MAOA interacted with adverse environment to form a vulnerability to antisocial spectrum behaviors in children, suggesting that the phenotype of antisocial behavior is much more than a sum of the genetic and environmental parts. However, these findings are difficult to replicate (43, 44), indicating that considerably more work is needed in this area to understand the relative contributions of genes, environmental influences, and their interactions.

13.3. Epidemiology

The prevalence of ASPD in the general population indicates strong gender differences, with higher incidence in men than in women. Using the Diagnostic Interview Schedule (2), the Epidemiologic Catchment Area study estimated ASPD prevalence to be 4.5% in men and 0.8% in women (45). Similarly, the National Comorbidity Survey (NCS) indicated substantial gender differences, with 5.8% of men and only 1.2% of women meeting ASPD criteria (46). In addition, ASPD prevalence rates tend to be similar across all races. For example, ECA estimates demonstrated little difference between African American and Caucasian races (2.3% vs. 2.6%, respectively), suggesting that ASPD tends to present with equal incidence across race and ethnicity (45).

In contrast to the substantial epidemiological research conducted for ASPD, studies of the prevalence of psychopathy are lacking in number and scope. Importantly, psychopathy prevalence estimates have previously been based primarily on incarcerated samples, thereby making comparison with general population ASPD epidemiology difficult. Many individuals in corrections settings meet the criteria for ASPD, thus raising the prevalence rates to 50% to 60% for incarcerated offenders (5). Psychopathy prevalence rates in prisons tend to be significantly lower than those for ASPD [estimated from 15.0% to 7.7% for men and 7.0% to 1.9% in women in corrections settings (7, 47)], leading researchers to believe that psychopathy must be quite rare in the broader general population. Low prevalence rates appear to be supported in empirical findings; the few epidemiological studies using psychopathy-specific criteria have estimated prevalence rates between 0.6% (48) and 3.6% (49), although these two studies were based upon the same small sample using different cutoff criteria.

It should be noted that these prevalence differences between ASPD and psychopathy, and the relative "rarity" of psychopathy, may be indicative of a confound between the criteria and the correctional setting. It has been suggested that the heavy weighting of the DSM-IV (and DSM-5) ASPD criteria toward criminal and delinquent behavior inflates ASPD prevalence in prison settings due to the nature of a correctional population (50). In addition to the behavioral elements of ASPD, the diagnosis of psychopathy is contingent on the presence of several personality traits (e.g., glib charm, arrogance) that would not necessarily be intrinsic to correctional populations. Because of this asymmetric criterion overlap, it is little wonder that 90% of incarcerated offenders who meet the PCL-R criteria for psychopathy also meet the behavioral criteria for ASPD, but as few as 30% of those with ASPD also meet the trait criteria for psychopathy (51). It may be that the widely accepted incidence differences between ASPD and psychopathy would cease to exist (or even be reversed) in other populations where the psychopathy traits of manipulation and glib charm are emphasized, such as the professions of law or politics (50).

Very few studies have exclusively focused on racial or gender differences in psychopathy prevalence. At this point, there is little evidence that psychopathy exists differentially across race in terms of how the construct validity is preserved (52–54) although a handful of studies have reported a higher incidence in African Americans than Caucasians or European Americans (55, 56). Gender differences in psychopathy prevalence are generally consistent with the ASPD findings (57), indicating that women are less psychopathic than men overall (58). Known gender differences in the facets of the FFM (59) may explain why. For example, Costa et al. (59) report that women score much higher on all facets of agreeableness and neuroticism than men, as well as on the warmth and positive emotions facets of the extroversion domain, and the dutifulness facet of the conscientiousness domain. Additionally, women score lower than men on the excitement seeking and assertiveness facets of extroversion. In sum, the facets in which the psychopath is low (see Definition section) are precisely those facets in which men tend to score lower than women (e.g., all facets of agreeableness, the anxiety, depression, self-consciousness and vulnerability facets of neuroticism, the warmth facet of the extroversion domain, and the dutifulness facet of the conscientiousness domain). Likewise, the facets in which the psychopath is high are facets in which men score higher than women (e.g., the excitement seeking and assertiveness facets of extroversion). That is, the facets of general personality structures involved in psychopathy are ones that are more characteristic of men than women. Thus, from a personality standpoint large gender differences in psychopathy are to be expected. Despite gender differences, evidence to date suggests that when clinical levels of disorder are present, psychopathy and antisocial traits look remarkably similar in presentation, and lead to similar outcomes (60, 61).

13.4. Clinical Picture

According to the DSM-IV (and DSM-5), a diagnosis of ASPD is contingent upon the early manifestation of conduct problems with onset before age 15 years, thereby documenting a stable and pervasive pathology. In adulthood, the antisocial individual has little regard for societal norms, and is often engaged in unlawful behaviors such as gambling, stealing, drug use, and destruction of property. Irresponsibility, recklessness, and impulsivity are hallmark features of ASPD. The antisocial individual is often unable to plan ahead, and generally fails to consider the consequences of his hedonistic actions to himself or others. This failure to construct organized plans and deliberate about the consequences of behavior creates pervasive instability in many areas of the antisocial individual's life, both in personal and professional domains. The employment histories of those with ASPD are often marred by unexplained absences and early terminations from jobs, and personal relations tend to be short-lived, and filled with strife and conflict. Further, antisocial individuals are often irritable and aggressive, leading to numerous physical and verbal altercations with others. Contact with the legal system is not uncommon for those with ASPD. Interpersonally, ASPD individuals are known to be remorseless, exhibiting little or no consideration for those whom they harm with their delinquent acts. In addition, those with ASPD are notoriously deceitful and manipulative, and are known for their ability to lie, con, and cheat others without detection.

As stated previously, the psychopathy criteria of the PCL-R have considerable overlap with the DSM-IV (and DSM-5) ASPD criteria. Both conceptualizations call for early diagnosis of conduct problems (although childhood conduct disorder is not in fact required for the PCL-R), and indicate several similar traits and behaviors, such as failure to plan ahead, impulsivity, delinquent and criminal behaviors, irresponsibility, remorselessness, and deceitfulness. However, the psychopathy criteria of the PCL-R also include a few personality characteristics absent from the DSM-IV (and DSM-5) ASPD criterion set, specifically glibness, arrogant self-appraisal, lack of empathy, and shallow affect (62). These indicators might suggest that the psychopath is more charming, self-assured, and cold-hearted than his ASPD counterpart, thereby making the psychopath seem both capable of, and successful at completing the most heinous of crimes.

An additional psychopathy criterion that has remained absent from both the ASPD and PCL-R conceptualizations is the absence of anxiety. According to Cleckley, the psychopath "appears almost as incapable of anxiety as of profound remorse," (3) (p. 340) and demonstrates "a relative immunity from such anxiety or worry as might be judged normal or appropriate" (p. 206). Many experts in the psychopathy field continue to support Cleckley's assertion that the psychopath is low in anxiousness (14) although this criterion ultimately failed to appear in the PCL-R due to poor item-total correlations (63). In sharp contrast to psychopathy, ASPD is said to be associated with high levels of anxiety and other affective disorders (1). The DSM-IV stated that individuals with ASPD "may also experience dysphoria, including complaints of tension, inability to tolerate boredom, and depressed mood" (p. 702) and may be prone to both anxiety and depressive disorders (1). While the presence of anxiety disorders may be an artifact of the psychiatric samples traditionally used to study ASPD, epidemiological studies also support the diagnostic comorbidity of ASPD and anxiety in community samples, suggesting that the relation is resilient beyond the clinical domain (64, 65). Thus, in the anxiety domain, the clinical pictures of psychopathy and ASPD are strikingly different in how they present. Further research is needed to better understand why these conceptualizations diverge in their respective relations to anxiety and to provide insight into whether this divergence is clinically meaningful to outcomes.

The inclusion of additional personality criteria in the psychopathy conceptualization also indicates that psychopathy has a heavier weighting toward the interpersonal and affective traits associated with crime than ASPD. The strong behavioral

focus of the ASPD criteria has received extensive criticism, as it makes the assumption that criminal behavior, rather than personality features, is a primary symptom of the disorder (5, 52). Hare makes explicit use of both behavioral and personality characteristics in the PCL-R, and has designated these domains as separate but equal through a two-factor structure. Hare's original PCL-R two factor solution characterized Factor 1 as consisting of the affective and interpersonal set of items termed the "selfish, callous, remorseless use of others", and Factor 2 as the behavioral criteria which he termed the "chronically unstable, antisocial, and socially deviant lifestyle" (52) (p. 79). Many studies have indicated that the ASPD criterion set correlates more highly with Factor 2 than with Factor 1 [e.g., (8, 62, 66, 67)], thereby supporting the heavy concentration of behaviors and the relative lack of personality characteristics in ASPD. However, while smaller than the relations with Factor 2, correlations between PCL-R Factor 1 and ASPD are significant, and indicate that at least some personality features are represented in both conceptualizations. In addition, studies of the ASPD criterion set have also indicated a two-factor structure, with facets that distinguish between the callous exploitation of others and impulsive disinhibition (68, 69), indicating that interpersonal characteristics play at least some part in the diagnosis of ASPD, albeit a more minor role. It should also be acknowledged that despite a concerted effort by the authors of the PCL-R to include distinct interpersonal and affective characteristics, much of the assessment of the PCL-R personality traits relies heavily on the existence and consideration of criminal behaviors. Due to this saturation of antisocial behavior, the PCL-R has received criticism comparable to the ASPD criterion set (12). To date, it remains unclear whether the PCL-R can be effectively applied within non-criminal settings, as the reliable assessment of antisocial activity becomes much more difficult in such populations.

While criminal and irresponsible behaviors appear to be important to the construct of psychopathy, some maintain that antisocial behavior deserves no role in the diagnosis of psychopathy whatsoever due to its role as a consequence, rather than a symptom, of the disorder (70). These authors argue that while trait descriptions of psychopathy characterize an individual who is prone to delinquency and antisociality, criminal behavior itself may arise from many alternative sources, with psychopathic personality being only one potential cause (71). By designating behavioral criteria as primary, rather than secondary symptoms, a diagnosis of ASPD may be given regardless of the actual genesis of the antisocial acts. Research using Structural Equation Modeling (SEM) supports a secondary hierarchical position for behavioral symptoms in psychopathy (72). Model fit estimates indicated that the simultaneous inclusion of behavioral items from the PCL-R (e.g., criminal behavior, criminal versatility, promiscuous sexual behavior) with impulsive, interpersonal and affective PCL-R items resulted in worse fit estimates than using impulsive, interpersonal and affective PCL-R items alone (72), and "actually degraded the measurement of psychopathy" with their inclusion (70) (p. 98). SEM fit estimates improved dramatically when behavioral items were placed as products (consequences) of the impulsive, affective, and interpersonal factors, leading Cooke and colleagues to argue that "it may be time to 'reconstruct' psychopathy by reducing or eliminating reliance on criteria that are overly saturated with antisocial and deviant behavior, thus putting personality back at the heart of this personality disorder" (70) (p. 99).

Work has begun in placing psychopathy back into the realm of personality. Trait-based alternatives to PCL-R assessment are beginning to gain credence, and demonstrate adequate reliability and validity as indicators of psychopathy (73). Among these are the Psychopathic Personality Inventory (9) and the FFM conceptualization of psychopathy (14), both of which have demonstrated positive associations with criminal and delinquent behaviors (9, 14, 74), convergence with other psychopathy measures (75, 76), and predicted relations to other known correlates of psychopathy including performance on laboratory tasks of aggression and deliberation (15). Thus, the assessment of psychopathy does not appear to be reliant on antisocial behavior, and can be achieved through a personality-based measure.

13.5. Pathology

Considerable research effort has been focused on the pathology of antisocial behavior. Within this domain, various proximal pathways to ASPD have been advanced, including psychoanalytic defenses, neuroanatomical abnormalities, psychophysiological arousal system impairments, deficits in cognitive functioning, and personality factors. Interestingly, rather than supporting one causal factor, this extensive research base indicates that many deficits are involved in antisocial behavior, leading to a very complex picture of pathology.

13.5.1. Psychoanalytic Defenses

The historical conceptualization of antisocial pathology comes from psychoanalytic thought. The antisocial individual was believed to suffer from "superego lacunae" or holes in the conscience (77). This superego pathology is associated with an "incapacity to experience self-reflective sadness" that ultimately results in callous, tough-minded behavior (78). This classical picture of the psychopath was modified in later conceptualizations, and is reflected in Cleckley's and Hare's descriptions of "semantic

dementia," where abnormal affective processing is the prime feature of the psychopath's pathology (3–5). Hare has described the psychopath as being "without conscience," a deficit that ultimately results in ruthless, manipulative, cold-hearted, and violent behavior (79). This prevailing and longstanding conceptualization of psychopathic pathology has pervaded the research, and has recently been extended into laboratory task designs (80). Studies assessing the psychopath's autonomic reaction to emotional words and fearful images appear to be supportive of abnormally deficient affective processing, although the psychopath's cognitive reports of emotional responses have been found to be similar to those of nonpsychopaths (5, 80).

13.5.2. Neuroanatomical Abnormalities

Structural and functional brain impairments have also been advanced as possible underlying pathologies of antisocial behavior (81, 82). Reviews of brain imaging studies of antisocial populations implicate abnormal functioning in the temporal cortex (83, 84), amygdala and hippocampus (85, 86), angular gyrus (87), and prefrontal cortex (87–89). Research in the psychopathy domain suggests much more widespread structural and functional issues, ranging from reduced volumes of the amygdala to abnormal shape of the hippocampus, and aberrant activity in all four lobes of the cortex (frontal, temporal, parietal and occipital), as well as several subcortical structures [see (90) for a review].

The neural dysfunctions implicated appear to be generally consistent with the existing research on both antisocial behavior and psychopathy. However, emerging research in this area suggests that there may also be subtle functional differences between psychopathy and antisocial behavior; work with children suggests that conduct disorder is associated with *increased* amygdalar activity in affective scenarios, but psychopathy is associated with *decreased* amygdalar activity in these same scenarios (91). Further, it has been demonstrated that for typical children and children with ADHD, unexpected punishment results in a reduction in ventromedial prefrontal cortex activity, whereas there is no such reduction for children with psychopathic traits (92). It may be the case that broad abnormalities are similar across disorders, but distinct areas of dysfunction exist, particularly for brain activity surrounding emotion and reward pathways.

While functional and anatomical deficits appear to be fairly replicable, causal conclusions have yet to be determined. Environmental factors may also play a part in creating neural abnormalities in antisocial individuals. For example, closed head injuries, drug and alcohol abuse, and early health factors may serve to exacerbate a genetic propensity, rather than act independently.

13.5.3. Psychophysiological Arousal System Impairments

Another influential theory of ASPD pathology comes from Gray's three arousal model of the nervous system (93). Briefly, this model entails the interaction of three neurophysiological arousal systems that are hypothesized to control behavior. The behavioral inhibition system (BIS) is said to inhibit behavior in response to punishment, in opposition to a behavioral activation system (BAS) that activates behavior in response to reward. The overarching nonspecific arousal system (NAS) can be activated by either the BIS or BAS system. Activation of the NAS generally results in an increase in arousal, with the valence of this arousal (inhibit or interrupt vs. approach) directed by the BIS or BAS. Within this context, normal, adaptive functioning is reliant on the balance of activation between the arousal systems. The observed symptoms of ASPD could be evidence of a malfunctioning BIS acting in concert with a normal or strong BAS (94, 95). In this manner, normal sensitivity and anxiety in response to threatening and stressful situations may be reduced or altogether absent in the antisocial individual. Low arousal may also be a factor in the observed deficits in feelings of guilt or remorse and may serve to increase resistance to aversive conditioning.

In support of Gray's model as applied to ASPD, many psychophysiological deficits have been associated with psychopathy. Lykken's (96) classical conditioning paradigm demonstrated that psychopathic inmates had abnormally low physiological responses (reduced skin conductance) to a conditioned stimulus paired with electric shock, indicating that the psychopath does not develop the expected anticipatory arousal from threat of physical punishment. Additionally, this conditioning showed a more rapid extinction in the primary psychopathic group when compared to secondary or "neurotic" psychopaths. Although low skin conductance is widely discussed in the literature, Raine's (97) review of this research indicates that this finding has not been altogether consistent. In contrast to Lykken's findings, contemporary research does not support group differences in skin conductance levels for psychopathic versus nonpsychopathic offenders (97). Interestingly, while low skin conductance has been associated with crimes of evasion [e.g., white collar crimes and customs offenses; (98)], it has not been found to be associated with other criminal activity, such as violent offenses (98). Additionally, although low skin conductance is associated with later institutionalization in behaviorally disordered children, it does not appear to be predictive of arrest (99).

Other autonomic arousal assessments have also been used to investigate psychophysiological functioning in the psychopath, including heart rate and startle response (100, 101). Low resting heart rate levels have been associated consistently with antisocial behavior in noninstitutionalized individuals, providing support for Gray's theory (97). However, studies of incar-

cerated populations generally fail to find group differences between psychopaths and nonpsychopaths, indicating that this finding may be a predisposing factor to antisocial behavior in general rather than psychopathy (97).

Some have argued that it is not generalized arousal deficits, but arousal deficits associated with the experience of emotion that best characterizes the psychopathic dysfunction (102). Interestingly, Casey, Rogers, Burns, and Yiend (2013) found that individuals with higher psychopathy scores were more autonomically responsive (as assessed by cardiovascular activity) when processing negative information, possibly indicating that psychopaths find unpleasant material somewhat rewarding (103). Emotionally valenced startle response tasks have also demonstrated reliable psychopathic psychophysiological deficits. Patrick, Bradley, and Lang (101) found that psychopaths do not show normal startle potentiation when viewing negatively valenced photos, although normal attenuation of startle was documented with positively valenced photos. Startle response deficits have been replicated numerous times, and may be considered supportive of a generalized deficit in behavioral inhibition dysregulation (104–107).

13.5.4. Deficits in Cognitive Functioning

Cognitive functioning deficits have also been implicated in the pathology of antisocial behavior. Historically, psychopathy has not been associated with "classic" cognitive dysfunction (e.g., intelligence, memory, executive ability), as the psychopath typically appears to be intact in most of these areas (3, 108). In fact, recent evidence indicates that violence is positively correlated with intelligence scores in psychopathic adults (109), and psychopathy scores are positively related to verbal, analytic, creative, and practical abilities in children (110, 111). However, the psychopath's notorious disconnect between successful planning and understanding of contingencies and subsequent violent, impulsive behavior indicates that a psychopathic cognitive deficit may exist, albeit in a more subtle form (112, 113).

Existing literature on the cognitive attributes associated with psychopathy indicates that the psychopath experiences stable deficits in the cognitive domains of attention (113, 114) and response modulation (115, 116). Laboratory task paradigms designed to assess the allocation of attention indicate that despite intact perceptual and autonomic processes, the psychopath is unable to switch attention from an ongoing task to secondary (or peripheral) information when appropriate (114, 117–119). The deficits in attention associated with psychopathy have been incorporated into the limbic dysfunction literature, and contribute to what Newman has coined the "response modulation hypothesis" (116). Many researchers believe that this may underlie the behavior control problems that characterize psychopathy (116). According to Newman, psychopaths continue approach behaviors even while maladaptive, and are unlikely to consider contextual information that may be helpful in choosing alternate responses (115). Newman, Patterson and Kosson (116) explored the inability of the psychopath to inhibit a dominant response to a card playing task of worsening odds and found that psychopaths continued for more trials of unlikely success with a dominant response set in comparison to nonpsychopaths. This effect has been replicated several times over, with different forms of stimuli and in conjunction with event-related brain potentials, and continues to a productive area of research in the pathology of psychopathy (116, 119, 120).

13.5.5. Personality Factors

Finally, personality differences are also considered an important aspect of the pathology of ASPD and psychopathy. Antisocial behavior has been associated with various personality traits and trait-like behaviors which are believed to underlie the construct, such as aggressiveness, impulsivity, sensation-seeking, lack of empathy, and impairments in cognitive functioning (14, 121). Eysenck's theoretical framework placed personality between the physiological processes of arousal and antisocial behavior, implying that personality moderates the relation (122). In other words, physiological functioning deficits may or may not develop into antisocial behavior depending on the personality characteristics present in the individual.

Indeed, Cleckley's description of the psychopathic personality is a testament to the importance of this aspect to the construct of ASPD. Since Cleckley's time, many other researchers have proposed personality-based models to understand psychopathy. Lykken's fearlessness hypothesis (96) proposed that the absence of anxious behaviors typically demonstrated by psychopaths is due to the psychopath's deficient emotional response to punishment or danger. In a description of this deficit, Lykken states that for the psychopath, "the fear of punishment and the coercive voice of conscience both are, for some reason, weak or ineffectual" [(123); p. 134]. According to Lykken, this absence of fear allows the psychopath to remain collected in high-stress situations, and inoculates against anxiety disorders. Rather than considering fearlessness as a correlate of psychopathy, Lykken considered it a precursor to the disorder.

Other models of psychopathic trait pathology abound, and have gravitated toward integrating dimensional models of personality with the psychopathy literature. Rather than focusing on individual characteristics, dimensional models of personality disorders incorporate the broad spectrum of personality to improve predictive capacity (124). By viewing psychopathy as a constellation of personality traits, the model can be used to subsume existent literature on the notable deficits associated

with ASPD and psychopathic pathology (16). The multifaceted nature of psychopathy is reflected in the varied pathology; simply put, different investigators are exploring different aspects of the psychopathy profile. For instance, the disinhibition and poor deliberation associated with response modulation deficits are likely representative of low conscientiousness, whereas the lack of empathy and ruthlessness of semantic dementia appear to represent low agreeableness or antagonism. Likewise, Lykken's fearlessness hypothesis seems to relate to hasty decision-making and recklessness, traits also associated with low conscientiousness. While an elegant conceptualization, the dimensional modeling of psychopathy remains in its early stages, and proposed mappings of traits to deficits have yet to be tested empirically.

13.6. Clinical Course

Although ASPD and psychopathy are considered pervasive disorders, the specific antisocial behaviors associated with these diagnoses tend to remit with age (3, 4, 125). Robins' influential longitudinal study of delinquent children indicated that approximately 40% of antisocial youths show a reduction in antisocial activity in adulthood, and that the median age of clinical improvement was 35 years (4). Similar findings have been reported in the psychopathy research, albeit with slightly higher age estimates for remission of symptoms (125, 126). In addition, cross-sectional prevalence estimates in prisoners reflect this trend with a linear decline in PCL-R and ASPD scores beginning at age 20 (127). Simply put, there appears to be a higher prevalence of ASPD and psychopathy in prisoners between the ages of 20 to 40 than after age 40. However, the clinical improvement documented is relative to the group; before the drop in criminal behaviors, psychopathic individuals participate in more criminal activity, have higher conviction rates, and serve longer sentences than nonpsychopathic offenders, and after age 40, conviction rates drop but remain comparable for psychopathic and nonpsychopathic criminals (125, 127). Thus, while the reduction of criminal behaviors over time is significant for the psychopath, this "improvement" merely renders them comparable in criminality to their nonpsychopathic counterparts.

Interestingly, while the psychopath appears to "age out" of his criminal activity over time, there is evidence that the personality characteristics that accompany psychopathy remain remarkably stable. In their cross-sectional study, Harpur and Hare (127) demonstrated that the psychopathy factors were differentially related to age; while Factor 2, which assesses the "traits and behaviors associated with an unstable and antisocial lifestyle" (p. 605) was found to have the predicted negative relation with age, Factor 1, which describes the "affective and interpersonal traits central to the classical clinical descriptions of the psychopath [including] egocentricity, manipulativeness, callousness, and lack of empathy" (pp. 604–605) was unrelated to age. In fact, Factor 1 scores of the 15–20 year-old age group were strikingly similar to Factor 1 scores of the 46–70 year-old age group, indicating that the personality characteristics present in Factor 1 show no significant age reduction. Thus, although criminal behaviors become less prevalent over the life course, the traits associated with psychopathy appear to continue to cause problems for the psychopath long after his criminal career ends.

The personality literature also supports these findings. Longitudinal studies of the NEO PI-R indicate that the factors of agreeableness and conscientiousness tend to increase across age (128). Importantly, these domains are those believed to be most important to psychopathy, ASPD, and antisocial behavior in general (15, 16, 124). Thus, independently of the psychopathy and ASPD research, predictions about the course of these disorders are supported from the broad personality literature.

13.7. Differential Diagnosis

Differentiation between ASPD and psychopathy and other DSM-5 diagnoses can be problematic as many other disorders may present with overlapping symptoms. For instance, the ASPD criteria of irresponsibility, aggressiveness, and impulsivity may also be associated with DSM-5 diagnoses such as schizophrenia, bipolar disorder, or major depression. In fact, longitudinal studies of delinquent children indicate that early conduct problems can sometimes be predictive of adult manifestations of schizophrenia, rather than ASPD (4). Conversely, the substance abuse and psychiatric malingering associated with ASPD and psychopathy may initially present as schizophrenia, also leading to difficulties in diagnosis. However, the antagonistic personality criteria (e.g., deceitfulness and lack of remorse), lack of psychotic symptoms, and pervasiveness of ASPD and psychopathy typically allow for sufficient differentiation between these disorders and most other DSM-5 diagnoses. Despite this, two disorders continue to cause concerns in categorical diagnosis of ASPD. Substance use disorder and narcissistic personality disorder remain difficult to distinguish from ASPD, and in fact substance use and antisocial behaviors have been shown to form a coherent "externalizing factor" according to epidemiological studies (129), suggesting that some variety of true overlap in pathology exists. For the purposes of this chapter, substance use disorders and narcissistic personality disorder will be discussed to identify potential divergence in diagnostic features and to inform treatment efforts.

Despite the relative reliability of the diagnostic criteria for ASPD, controversy remains about the adequate differentiation between ASPD/psychopathy and substance use disorders. Comorbidity estimates indicate that ASPD is strongly associated

with substance use disorders (1), and in the ECA study, 84% of those diagnosed with ASPD also reported some form of substance use or abuse (64). Additionally, PCL-R scores are strongly associated with substance use, particularly with Factor 2 of the PCL-R (130). However, the comorbidity estimates reported may be indicative of overlapping criterion sets (131); the history of those involved with dyscontrolled drug use generally include some of the same traits and behaviors associated with ASPD and psychopathy, including theft, deception, poor work history, and irresponsibility. Thus, differentiation between the disorders remains difficult. While suggestions have been made to incorporate exclusion criteria for DSM-IV ASPD in lieu of substance use disorder presence (132), the early onset of behavioral problems specific to ASPD (versus the lack of early onset for substance use disorders) has been presumed to be an adequate differentiation criterion, ultimately preventing a substance use exclusion criterion from being included in revisions of the DSM (50). On the other hand, both disorders appear to share a common underlying pathology and course (133, 134), and each may contribute to the development of the other, making the use of the early onset criterion a troublesome differentiation factor.

The other psychiatric diagnosis that is often reported to be comorbid with psychopathy and ASPD is narcissistic personality disorder [NPD; (135, 136)]. In contrast to the criterion overlap with the irresponsibility and antisocial behaviors associated with substance use, NPD appears to share the manipulative, exploitative, and callous traits associated with ASPD and psychopathy. In support, PCL-R total scores and Factor 1 scores correlate significantly with NPD, but Factor 2 scores do not (66), a pattern of correlations that is the mirror image for ASPD. While the clinical and theoretical literatures of NPD and ASPD/psychopathy have grown independently, psychodynamic views generally incorporate narcissism into the psychopathy conceptualization (137, 138). In fact, many have explicitly suggested that NPD is a lower-order facet of the psychopathy construct, and have argued that NPD is a closer conceptualization of psychopathy than ASPD (139). However, due to concerns about diagnostic overlap and differentiation, authors of the DSM-IV ultimately decided to incorporate components of the PCL-R (i.e., lack of remorse) into the ASPD criterion set to increase the validity of the assessment of ASPD within prisons and other forensic settings (140).

From a personality standpoint, the diagnostic comorbidity and poor differentiation between personality disorders is understandable, and even predicted. Dimensional models of ASPD and psychopathy indicate that these disorders obtain diagnostic comorbidity with other DSM-IV (and DSM-5) personality disorders to the degree that they share overlapping constellations of personality traits (141). Lynam and Derefinko (142) conducted a comparison of predicted comorbidity (based on expert-generated personality prototypes) and empirical comorbidity between the psychopathy and the DSM personality disorders. Expert prototype predictions indicated that psychopathy would share the highest comorbidity with ASPD (with shared low agreeableness and low conscientiousness), followed by NPD (with shared low agreeableness). These predictions were supported by meta-analytic results of empirical findings (142).

13.8. Treatment

There is considerable debate surrounding the efficacy of treatment for ASPD and psychopathy (143). Although some treatment-outcome research has indicated positive results for therapeutic interventions (144–147), other empirical evidence appears to suggest that the antisocial behaviors associated with ASPD and psychopathy are resistant to intervention, particularly for the psychopath (148–150). Authors on both sides of the argument cite significant shortcomings in the existing treatment-outcome research, such as the lack of control groups, the use of clinically insignificant outcome measures, the use of inappropriate treatment strategies, high variability in results, and the clinical (vs. statistical) meaningfulness of effect sizes (143, 147, 151, 152). All of these factors contribute to the confusion about whether treatment of those with ASPD and psychopathy is a viable pursuit, or should be abandoned in favor of traditional management through incarceration.

Several studies indicate that psychopaths benefit less from treatment than nonpsychopaths, demonstrating higher attrition rates, lower clinical improvement, higher violent recidivism, and more immediate recidivism upon release than their nonpsychopathic counterparts (153–155). In addition, high PCL-R scores (particularly Factor 1 scores) have been associated with significantly higher recidivism rates in treated psychopaths than untreated psychopaths, suggesting that psychopaths actually get worse with therapy (148, 149, 156). Thus, it is generally accepted that "nothing works" with respect to treating psychopathy (157); the psychopath seems to benefit less from treatment than nonpsychopaths, and in some cases, therapeutic interventions appear to increase future criminal activity in the psychopath, indicating that management, rather than treatment, may be the prescribed course for this type of offender (158).

This pessimism regarding treatment is enhanced by the over-reliance on findings of a handful of landmark studies that report notably disappointing outcomes (159). This is unfortunate, given that some of the studies cited are of questionable scientific value. For instance, in the most famous treatment outcome study of psychopathy, the Penetanguishene study, Harris and colleagues (148) reported that therapeutic community (TC) treatment significantly increased recidivism in psychopaths compared to the untreated psychopathic group (77% vs. 55%, respectively). However, the TC treatment employed in this study was an unlikely candidate for success; the "total encounter capsule" involved nude encounter groups, feeding through tubes in the

walls, and LSD and alcohol administration for many days at a time [(148)pp. 285–288]. Remarkably, the Penetanguishene study continues to be used as evidence that treatment of the psychopath is contra-indicated. Perhaps even more surprisingly, although it seems apparent that therapeutic communities are not effective at reducing future criminal behavior (160, 161), they remain popular in prisons and psychiatric hospitals in Europe (143). But perhaps it is not surprising that unconventional therapies are often used. It is recognized that the characteristics of antisocial individuals create very difficult obstacles for treatment, thereby limiting the number of available options for intervention. While pharmacological research suggests that specific symptoms of ASPD can be effectively reduced through medication (151, 162), concerns about compliance outside of controlled settings and the high potential for abuse associated with some substances inhibits the degree to which this type of treatment can be used. For instance, while dopaminergic stimulants such as methylphenidate have been found to improve symptoms of inattention, irritability, conduct problems, and impulsivity in adults and adolescents with antisocial behaviors (163–165), the comorbidity between ASPD and substance abuse limits the use of this intervention beyond controlled settings due to its high potential for abuse when appropriate use of this medication cannot be monitored (151).

Other pharmacological treatments have also shown promise in the reduction of the aggressive behaviors associated with ASPD and psychopathy, but may also be limited in their use due to concerns about long-term treatment compliance (166, 167). Lithium has received considerable attention for use in those with ASPD due to its efficacy at reducing impulsive violent behaviors in nonbipolar adults and adolescents (168, 169). Additionally, selective serotonin reuptake inhibitors (SSRIs) such as sertraline and fluoxetine have been associated with significant reductions in overt hostility, aggression, and antisocial behavior (170–172), as have anticonvulsants, including valproic acid (173), or its salt form, divalproex sodium (174, 175), and phenytoin (176). Like methylphenidate, the use of lithium and antipsychotics to control aggression is suitable in forensic settings, but the poor treatment compliance demonstrated by those with ASPD may reduce the effectiveness of this treatment in the long-term (166, 167).

In addition, the manipulative and remorseless traits associated with psychopathy do not bolster optimism for therapeutic interventions. Some researchers believe that despite good compliance with therapy and reported therapeutic improvement in correctional settings, the psychopath is simply using what he uses in therapy to enrich his criminal versatility and skill, thus accounting for negative outcomes (143). For instance, structured cognitive-behavioral techniques designed to target the behaviors associated with ASPD and psychopathy have demonstrated insignificant, or even inverse relations with recidivism, despite reported therapeutic gains such as conduct during sessions and therapists' ratings of motivation ((149); see (143) for a review). Radical therapeutic change techniques aimed at modifying the character of the psychopath have been proposed, but to date, have limited empirical support (177). One example of this type of treatment is Cloninger's (151) coherence therapy which is designed to address the unseemly character of those with ASPD in the hopes of increasing "trust, hope, and compassion" in the remorseless individual. Cloninger (151) posits that deficiencies in self-transcendence and emotional awareness underlie antisocial traits, and can be improved through meditative exercises, exposure to classical music, and therapeutic exercises in self-efficacy. While many agree that therapy targeting dysfunctional characteristics may be a very important aspect of the treatment of those with ASPD, it is perhaps unrealistic to expect self-transcendence exercises to be the most effective way of eliciting this type of change (178).

In contrast to those who hold little hope for changing the outcomes of those with ASPD and psychopathy, some authors contend that the treatment of ASPD and psychopathy can be beneficial, and that the reported failures in treatment response are simply not the norm (147, 151, 159). In fact, large meta-analytic studies indicate that many forms of treatment (e.g., electroconvulsive therapy, psychodrama, cognitive-behavioral therapy, psychoanalysis, therapeutic communities, and pharmacotherapy) have a positive overall effect on the reduction of recidivism for adult offenders (147, 179, 180), and juvenile offenders alike (181, 182). In addition to overall effect sizes, Lipsey (181) conducted moderator analyses on over 400 treatment-outcome studies to identify important factors that contribute to therapeutic success; reductions in criminal recidivism are associated with greater therapeutic intensity (longer duration and more frequent contacts), structured treatments (e.g., cognitive-behavioral therapy and skills training), and multimodal treatments (e.g., individual and group therapy coupled with vocational training, pharmacological treatment and work assignments). Thus, the quantitative treatment results appear to indicate something quite different than the dismal conventional standard. When specific guidelines are followed, it appears as though significant gains can be attained (159, 182).

Many of these same techniques have been recommended in a recent review of treatment outcomes for psychopathy (152). Salekin and colleagues suggest several possible "practical problem areas" (p. 256) when conducting therapy with psychopathic individuals, including addressing motivation to change, deceptiveness/manipulativeness, and lack of emotion and empathy leading to poor attachment, as these appear to be areas that prevent optimal outcomes. However, this review also noted that of the recent treatment studies, only 3 of 8 adult studies indicated any success. This same review identified 8 recent studies of treatment in psychopathic youth, and unlike the adult outcomes, youth treatment seemed much more effective; 6 of 8 studies indicated some therapeutic gain in terms of recidivism and latency to recidivism suggesting that early intervention is likely to be the best practice in terms of instituting relevant changes (152).

However, even though individual studies and some meta-analytic work indicates that treatment has a positive influence on recidivism, it is still questionable whether these are truly meaningful gains. Importantly, reported effect sizes in this area tend

to gravitate toward a value of .20, which is comparable to that of a placebo effect (179–183). The clinical meaningfulness of this improvement may simply be insignificant. For instance, the treated offender may have committed rape fewer times in the five years following release than the untreated offender, but the fact that he continues to rape (albeit with less frequency) speaks to the inadequacy of contemporary interventions. Although modest reductions in antisocial behavior are important, these reductions do not indicate that treatment is eliciting substantive change. In addition, many of the studies used in meta-analytic research of the treatment of ASPD and psychopathy rely on one group, pre-post treatment designs (143). This type of study design has been found to overestimate treatment effects, thereby making these positive effect sizes even less convincing (182). Finally, very few treatment studies have examined long-term efficacy of treatments, reporting primarily on short-term outcomes. This can result in the inflation of positive results, as well as mask discouraging survival statistics. As can be seen in a recent study by Olver, Lewis, & Wong (184), even large therapeutic treatment gains in the short-term may not have lasting effects; of 38 incarcerated offenders with high psychopathy scores who responded well to treatment, only 10% had violently recidivated during the first year post-treatment. However, this number increased to over 60% within 10 years (184). Thus, while meta-analytic results provide compelling suggestions that treatment interventions addressing the criminal behaviors of ASPD and psychopathy should continue to be pursued, they do not actually document that contemporary programs are having a substantial, meaningful effect.

In sum, clear conclusions about the efficacy of treatment for ASPD and psychopathy are difficult to draw. While meta-analytic findings appear to support further investigation into treatment interventions, they also fail to fully contradict the argument that these disorders are largely unresponsive to treatment in general. Although even mild to moderate changes in antisocial personality traits can be associated with benefits to the person and to the wider society, the relative modesty of therapeutic gains indicates that treatment needs to improve before we can decisively conclude that ASPD and psychopathy are treatable disorders.

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14
Alcoholism

Afshan Anjum, M.D.*

Abstract The use of alcohol is woven into our culture in a most complex fashion. The majority of adults in the United States consume alcohol, yet alcohol also causes nearly 100,000 deaths per year and cost the society $223.5 billion in 2006 alone. Harm from alcohol can occur in a number of ways. First, if alcohol is consumed above a certain threshold, on the order of one drink/day for a woman or two drinks/day for a man, medical consequences, e.g. hypertension, cirrhosis, or depression, can occur over time. Second, if alcohol is consumed to the point of intoxication and impairment, the risk of domestic violence and child abuse, motor vehicle accidents, criminal behavior, and problems at work or school are greatly increased. Third, in susceptible individuals, alcohol use leads to the development of a true addiction to alcohol—alcoholism. Alcoholism is characterized by loss of control over alcohol use, compulsive use, and the development of physical dependence. The negative consequences of alcoholism are generally severe.

Alcoholism, or alcohol dependence, was first suggested to be a disease in the 1780s but only recognized as such by the American Medical Association in 1958. The diagnostic criteria for alcoholism have shifted somewhat over time but the core elements of loss of control, compulsive use despite adverse consequences, and physical dependence remain. Alcoholism is a common disorder with a lifetime prevalence of 20% in men and 10–15% in women (1). The etiology of alcoholism involves biopsychosocial components with an estimated 50% of risk coming from genetics. Alcoholism and unhealthy alcohol use are under-recognized by clinicians though a variety of medical symptoms and laboratory findings or positive answers to simple questions should alert the clinician to alcohol-related problems. Alcoholism should be viewed as a chronic disease; individuals are not "cured". However, alcoholism is a treatable disorder and many patients achieve long-term sobriety or greatly reduce their use of alcohol. Treatments for alcoholism include a variety of psychosocial techniques such as brief intervention, relapse-prevention therapy, and traditional residential programs. Alcoholics Anonymous is a self-help organization that has helped many alcoholics. Recently, medications that target neurobiological factors involved in relapse have become available—naltrexone and acamprosate. The evolving treatment of alcoholism includes an integration of psychosocial interventions with medication coupled with awareness that treatment requires long-term management.

Keywords Alcohol dependence · Alcohol abuse · Treatment · Diagnosis · Brief intervention · Naltrexone · Acamprosate · Genetics

14.1. Definition

Alcoholism (alcohol dependence, alcohol addiction) was first described as a disease by Benjamin Rush in the United States and Thomas Trotter in England in the late 1700s (2). The concept that a pathological use of alcohol is a disease was quite novel and in opposition to the idea that alcoholism represents a moral problem or a deficiency in will power. However, acceptance of the disease model of alcoholism has not been straightforward and it was not until 1958 that the American Medical Association

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A. Anjum, M.D. (✉)
Assistant Professor, Department of Psychiatry, University of Minnesota School of Medicine,
Minneapolis, MN, USA
e-mail: anju0001@umn.edu

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recognized it as such. The lay population and the medical community continue to have varied perspectives regarding the disease concept of alcoholism.

The diagnostic criteria for alcoholism continue to evolve. The successive editions of the American Psychiatric Association's Diagnostic and Statistical Manual of Disorders since 1980 reflect changing opinions about what elements in the definition should be emphasized. The 1980 DSM-III emphasized problems from drinking (called substance abuse) and specified that the term alcohol dependence (the officially preferred term for alcoholism) required evidence of physiologic tolerance and/or withdrawal. These criteria for abuse and dependence drew considerable criticism, and in 1987, the criteria were revised in DSMIIIR with greater emphasis on patterns of compulsive use and less emphasis on dependence and withdrawal. DSM-IV (3) criteria resembled those in DSM-IIIR in not making physiologic dependence essential to the definition of the disorder, but the order of the criteria was changed so that items related to dependence were listed at the outset.

The criteria for alcohol dependence presented here are from the DSM-IV criteria for Substance Dependence.

In DSM-IV, published in 1994, substance abuse was categorized under two distinct disorders of abuse and dependence with separate criteria for each disorder (3). Abuse and dependence were seen on a continuum with more severe illness with legal repercussions being labeled dependence which probably was the closest term used to describe alcoholism. The DSM IV-TR was published in 2000 and contained additional information on the diagnosis (4). Under the new DSM-5 criteria released May 2013, alcohol abuse is categorized under the overarching diagnosis of substance abuse disorder which is defined by 11 different criteria and categorical distinction ranging from mild to moderate to severe based on the severity of alcohol use (5). The legal consequence criterion included in DSM-IV has been dropped and a new craving criterion has been added. Thus, based on DSM-5 definition, if a person exhibits any two symptoms from a list of 11 criteria, during the same 12-month period, he/she is diagnosed as having an alcohol use disorder.

It is highly unlikely that alcoholism is a unitary disease. Fifty years ago Jellinek described subtypes of alcoholism that varied based on severity, use patterns and prognosis (6). We continue to revise and refine our definitions of alcoholism with awareness that there are likely several forms of alcoholism. As discussed below, scientific advances should allow us to eventually classify alcoholism more precisely—based on a clearer understanding of the genetic and pathophysiologic disease processes.

14.2. Epidemiology

Epidemiologic studies of alcohol use and abuse are bedeviled by the uncertainties of what to measure and how to measure it. Prevalence rates for a disease are, of course, dependent on the current definition for that disease. For alcoholism, there has been no absolute and unchanging reference point. Therefore, the trends in alcoholism prevalence over time are difficult to accurately assess. Nevertheless, modern epidemiologic tools targeted towards the general population provide us with a broad picture of the landscape of alcohol use, misuse, and alcoholism and give a sense of the extent of the problem. For the purposes of this chapter epidemiologic studies focused on the United States will be reviewed.

14.2.1. Consumption

The United States is a drinking culture. Recent population studies indicate that 60–65% of the adult population report consuming alcohol in the past year (7). Average consumption, based on sales, for adults (ages 14 and older) was 2.23 gal of ethanol in 2004, and 2.31 in 2007. (www.niaaa.nih.gov/Resources/DatabaseResources/QuickFacts/AlcoholSales/consum01.htm). Average consumption had been trending downward since the 1970s but has had a slight increase since 2000.

One of the more concerning issues regarding consumption is the prevalence of binge drinking, particularly among young people. Binge drinking is defined as consumption of five or more standard drinks in a row for men or four or more for women. A standard drink is considered 12 oz of beer, 5 oz of nonfortified wine, or 1.5 oz of liquor and, in the United States, to contain 12–14 g of ethanol. Among US adults surveyed in 2011 using behavior risk factor surveillance system (BRFSS), 18.3% reported binge drinking an average of four times per month and consumed approximately eight drinks per episode (http//www.appsnced.cdc.gov/brfss). Studies in college students reveal an increasing trend in binge drinking. Weschler et al. (8) reported that 44% of college students reported binge drinking in the 2 weeks prior to completing a screening questionnaire ($n = 14{,}138$). Over half of the binge drinkers reported binge drinking three or more times over 2 weeks—identified as frequent binge drinkers. Disconcertingly, frequent binge drinking was significantly higher in the 1999 population compared to samples questioned in 1993 and 1997. In the overall U.S. population, survey studies indicate that about 36% of men and 16% of women ages 18 years or older report at least one binging episode (five or more drinks) in the previous 30 days (9). The average number of binge episodes per year was 20.1 in men and 5.8 in women. Binge drinking is, understandably, more prevalent in heavy drinkers but 72.9% of binge drinkers are moderate drinkers. Binge drinking is of particular concern to society and to clinicians because, regardless of whether a formal alcohol use disorder is present, it is associated with increased morbidity, mortality, and social problems such as accidents, crime, and absenteeism.

14.2.2. Prevalence of Alcohol Abuse and Alcohol Dependence (Alcoholism)

Results from the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC), a population survey of 43,093 adults in the United States, conducted in 2001–2002 revealed that the 12 month prevalence rate of DSM-IV defined alcohol dependence was 5.42% for men and 2.32% for women (10). Lifetime rates were 17.18% for men and 7.84% for women (11). Twelve-month prevalence rates were highest in the 18–29 year old range and declined with increasing age. 12 months rates for abuse were 6.93% in men and 2.55% in women (10).

A second wave of NESARC survey was conducted from 2004 to 2005. These surveys and data obtained were unique in that there was a 81% response rate, with people from all walks of life being surveyed and minorities were oversampled to examine the impact of race and ethnicity on comorbidity and access to health care (11). Trends for alcohol use were observed overtime and compared between 1991 and 1992 vs. 2001 and 2002. Alcohol abuse was reported to have increased to 4.6% from 3.03% and dependence decreased to 3.81% from 4.38%.

14.2.3. Morbidity and Mortality Attributable to Alcohol

Morbidity and mortality associated with alcohol is considerable. The Center for Disease Control reports that, for the period of 2006–2010, in the United States, excess alcohol consumption contributes to 88,000 deaths/year and that excessive alcohol use is the third leading cause of lifestyle-related death (http://www.cdc.gov/alcohol/quickstats/general_info.htm). Alcohol is a major contributor to domestic violence and other crimes, to child maltreatment, and to traumatic injuries. In 2005, nearly 17,000 individuals died in alcohol-related traffic accidents.

The medical consequences of alcohol are broad. Alcohol affects nearly every organ system in the body including the brain. A patient does not need to meet criteria for alcohol abuse or dependence in order to develop deleterious consequences from alcohol consumption. It is incumbent upon clinicians to consider a role for alcohol in many medical or behavioral problems. One of the challenges to interpreting the health consequences of alcohol for the clinician and lay public alike is the evidence that low levels of alcohol consumption can reduce the risk of coronary artery disease and stroke (12). This evidence has sometimes been referred to as the "red wine" benefit and is frequently noted in the lay media. This effect has often been misinterpreted that since alcohol can be good for you, its risks are not that serious.

14.2.3.1. Medical Illness

There is a vast literature devoted to the medical consequences of alcohol. The interested reader is encouraged to consult traditional medical textbooks or medical journals for more information on this topic. Epidemiological studies have attempted to estimate the relationship between levels of consumption and various illnesses (13, 14). Low-moderate levels of alcohol consumption in the 1–2 drinks/day range are associated with lower risk for coronary heart disease and ischemic stroke, but this is balanced by increased risk for other disorders including liver cirrhosis, essential hypertension, pancreatitis, gastroduodenal ulcer, hemmorhagic stroke, and several types of malignancy including breast cancer. Though some benefit for coronary heart disease remains evident at alcohol consumption levels of 3–4 drinks/day, the risk for other disorders increases significantly as higher levels of alcohol are consumed. For example, the relative risk for cirrhosis goes from 2.9 at 25 g alcohol (~2 drinks)/day to 7.1 at 50 g alcohol (~4 drinks)/day to 26.5 at 100 g of alcohol (7–8 drinks)/day) (14). Women develop medical consequences from alcohol at lower total consumption levels than men and their disease progression is faster than men (15).

Alcohol is involved in approximately 50% of fatal motor vehicle crashes, 17–53% of fatal falls, 37–64% of fatal burns, and 38% of fatal drownings (16–18). It is likely that alcohol's relationship to these traumatic deaths is significantly underreported.

14.2.3.2. Alcohol, Structural Brain Damage, Cognitive Impairment, and Dementia

A relationship between excessive alcohol consumption, cognitive impairment, and frank dementia has been noted for years. Whereas nutritional deficiencies, particularly thiamine, have been shown to be essential for some forms of alcohol-related dementia, e.g., Korsakoff's syndrome, there is increasing evidence that alcohol can induce structural brain changes and cognitive impairment independent of thiamine deficiency. The development of noninvasive brain imaging techniques has led to a wealth of findings regarding brain changes in alcoholism [see (19) for review]. Noteworthy are loss of cerebral cortical mass (particularly prefrontal cortex) and cerebellar atrophy along with subcortical white matter loss and atrophy of other structures including hippocampus, striatum, and thalamus as shown in Fig. 14.1 (19). Paralleling these structural changes are neuropsychological deficits particularly in gait and balance, executive function, and visuospatial abilities. The deficits in executive function may contribute to the disease process by interfering with a patient's ability to change behavior.

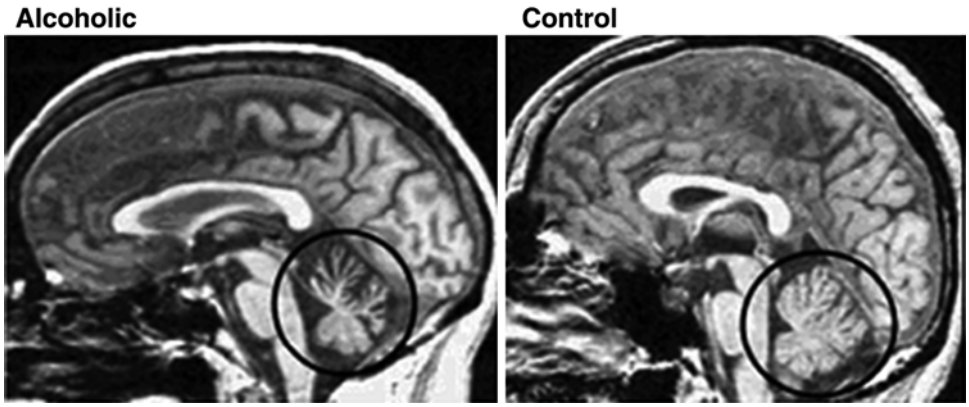

FIGURE 14.1. Midsagittal view of an MRI of the brain of an alcoholic, showing severely shrunken folia of the anterior superior vermis compared with an age-matched control man. With kind permission from Springer Science + Business Media: Psychopharmacology (Berl), Neurocircuitry in alcoholism: a substrate of disruption and repair, volume 180, 2005, pages 583–594, Sullivan EV, Pfefferbaum A, Fig. 2.

14.2.3.3. Alcohol Induced Psychiatric Disorders

There is extensive comorbidity of alcohol dependence with psychiatric disorders. The Epidemiologic Catchment Area study completed in the 1980s indicated that 37% of individuals with an alcohol use disorder had a comorbid mental illness (20). In many cases, the use of alcohol is thought to precede the psychiatric disorder and lead to a secondary psychiatric disorder or substance-induced disorder. However, it is often a challenge to sort out the primacy of alcoholism vs. another psychiatric illness and many times it simply cannot be done.

Depression is one of the most common consequences of heavy alcohol use. In a study of patients admitted for alcoholism treatment, Brown and Schuckit (21) found that 42% had Hamilton Depression Rating scores higher than 20 in the first week of admission—a level compatible with significant depression. Inpatient treatment and supportive care without the use of antidepressants was associated with a marked reduction in depressive symptoms with only 6% of patients having significant symptoms by week 4. Of course, as noted by the authors, rating scales for depression indicate presence of sleep and appetite problems, somatic symptoms, and anxiety symptoms, as indicators of the severity of depression. Withdrawal from chronic alcohol use, especially in hospitalized patients, is associated with disturbances in these same domains leading to false-positive assessments of depression. Nevertheless, depressed mood, guilt and suicidal ideation and attempts—core symptoms of depressive illness—are common in alcoholic patients and it is clear that, in some patients, alcohol induces a true depressive disorder.

Insomnia has been reported to occur in anywhere from 36 to 72% of alcoholic patients (22). Sleep problems vary across the cycles of alcohol use and binging, acute alcohol withdrawal, and protracted alcohol withdrawal. Key sleep findings during abstinence include initial insomnia, reduced total sleep time, reduced slow wave sleep, and disturbances in REM sleep (23). Sleep disturbances can normalize with sobriety though this may take months (24).

Anxiety is a common symptom of alcohol withdrawal and may persist for an extended time. There is basic science evidence that alcohol can induce anxiety-related behavior and that this may relate to relapse (25). Differentiating alcohol-induced anxiety from primary anxiety disorders is challenging and anxiety disorders should be carefully screened for in all alcoholic patients (26).

Suicide is a significant risk factor in alcoholism. One estimate is that up to 40% of alcoholic subjects will attempt suicide and 7% of alcoholics will end their lives by suicide (27). A number of risk factors have been identified in alcoholic patients that increase the chance of a suicide attempt including being male, having a comorbid major depression or significant medical illness and living alone (27).

14.2.3.4. Fetal Alcohol Spectrum Effects

The consequences to the fetus of maternal alcohol consumption include a number of neurobehavioral deficits and physical abnormalities collectively referred to as fetal alcohol spectrum effects (FASEs) (28). The classic fetal alcohol syndrome (FAS) is associated with developmental abnormalities including a triad of dysmorphic facial features, growth retardation and central nervous system abnormalities. The facial dysmorphic features include thin upper lip, nearly absent philtrum, and small palpebral fissures. Cognitive and behavioral impairments include overt mental retardation as well as deficits in more specific domains such as executive function, attention/hyperactivity, and social skills. FAS is a significant cause of mental retardation and one that is completely preventable. Although there have been major public health efforts to educate women about the risks of drinking

during pregnancy, the CDC estimates that 3% of pregnant women drink at levels associated with FASEs (29). Physicians should counsel all women to the potential danger to their fetuses of drinking during their pregnancy. The frequency of binge drinking among young women represents another concern for FASEs because binge drinking in the early phase of fetal development, when some women are unaware that they are pregnant, is associated with FAS.

14.3. Clinical Picture

The clinical presentation of the alcohol-dependent patient is contingent on when in the course of the illness he or she presents. There are no pathognomonic signs or symptoms of alcohol abuse or dependence. Although medical symptoms may bring an alcoholic into his or her first contact with a possibility for therapy, early in the course of the illness there may be no physical or laboratory signs of this condition. Additionally, physician discomfort, judgmental attitudes, or inadequate training and patient denial raise additional barriers to effective diagnosis. Often, indications of an alcohol problem can be gained only through a careful social and medical history. Specific inquiry regarding marital conflict, absenteeism from work or school, job losses, accidents, and legal difficulties should be made; such problems occur more commonly in alcoholics than in nonalcoholics. Patients who indicate that they have such problems should be asked about the relationship of alcohol to the problems and about specific drinking practices. Not infrequently, the alcoholic will deny or rationalize the relationship of alcohol to his or her problems and will underreport the quantity of alcohol consumed. If willing to admit to problem drinking, the early alcoholic may report sneaking drinks, hiding alcohol, feeling comfortable only with other drinkers, experiencing guilt associated with drinking, and attempting to control drinking by using alcohol only at specified times (30).

Medical complaints early in the course of alcoholism include anorexia, morning nausea and vomiting, gastroesophageal reflux, diarrhea, palpitations, insomnia, amenorrhea, impotence, and polyuria. Psychiatric and neurologic complaints may include depressed mood, anhedonia, insomnia, anxiety, irritability, nervousness, blackouts (memory lapses), and subjectively poor memory (31–33).

Early in the course of alcohol use, hypertension can occur with as few as three drinks per day, with higher consumption associated with higher blood pressures (34). An estimated 5–24% of hypertension is associated with alcoholism (34); thus internists should screen all hypertensives for possible alcoholism, and psychiatrists should measure blood pressures regularly and consider an alcoholism diagnosis in hypertensive patients. The physician should be aware that blood pressures can decline and rise in tandem with active drinking.

As alcoholism progresses, physical signs may begin to appear, such as an alcohol odor on the breath, careless grooming and hygiene, signs of intoxication (ataxia, slurred speech), multiple traumas, hepatomegaly (31), and certain facial features, including rhinophyma and persistent erythema, with or without telangiectasias. Later in the course, signs of chronic liver disease may appear, including jaundice, ascites, palmar erythema, spider angiomata, purpura, abdominal varices, testicular atrophy, gynecomastia, and Dupuytren's contractures. Associated symptoms of liver, pancreatic, and other chronic gastrointestinal disturbances may be reported, including abdominal pain, food intolerance, hematemesis, melena, weight loss, weakness, and fatigue.

Neurologic and psychiatric signs and symptoms may occur in later-stage alcoholism and include seizures (unrelated to active drinking or withdrawal), withdrawal syndromes (seizures, hallucinations, delusions, delirium), psychotic syndromes (paranoia, hallucinations, and delusions in a clear sensorium), peripheral neuropathy (usually in the lower extremities, bilateral, symmetrical, and sensorimotor in type), and cognitive deficits (ranging from minor memory problems to dementia and the anmestic syndrome) (35–39).

Uncommonly, myopathy may occur acutely with muscle pain and swelling or chronically with progressive weakness and atrophy. Also, rarely, cardiomyopathy may occur with signs and symptoms of congestive heart failure.

As noted earlier, certain psychiatric diagnoses, including antisocial personality, mania, drug abuse, panic disorder, depressive disorder, and schizophrenia, are found more frequently in conjunction with alcoholism than in patients without these disorders, and hence patients with these diagnoses should raise a psychiatrist's index of suspicion that alcoholism also may be present (40).

It is important to emphasize that early phases of the disease may be marked by subtle or no physical, psychiatric, or laboratory signs and thus require a high index of suspicion by the physician coupled with a sensitive and thorough approach to history taking.

14.4. Case History

J. W., a 35-year-old plant foreman, arrived at his physician's office with chief complaints of 3 weeks of intermittent epigastric pain, anorexia with a 5-pound (2.3-kg) weight loss, and nausea and vomiting. He related that these symptoms were worse in the morning and improved as the day progressed. He indicated that he was not too worried by the symptoms but had come at the urging of his supervisor, who was concerned because of his frequent absences from work.

He denied all other gastrointestinal symptoms, and review of systems was negative except for numerous—colds-in the past year, causing frequent work absence. Physical examination was within normal limits.

When questioned about his drinking practices, he said that he drank—"no more than anyone else." When asked to elaborate, he stated that he went to a local tavern with fellow employees after work for "a few beers" and drank "a six pack or two on the weekends while watching football on TV." When asked about drinking at other times, he replied, "That's all. Why do you keep badgering me about my drinking?" He was then asked if others badgered him; he answered, "Yes, my wife-she thinks everybody drinks too much. Just because I was arrested for driving under the influence last year … but I'm here for my stomach, Doc. Can you help me?" He was scheduled for routine laboratory tests and endoscopy and was asked to return in 1 week.

J. W. may or may not be an alcoholic, but the pattern of his symptoms and his responses to questions about his drinking habits should raise his physician's index of suspicion.

14.5. Laboratory Findings

As is true of signs and symptoms, there are no pathognomonic laboratory measures that can be used to diagnose alcoholism. There are a number of laboratory findings, however, that, when present, should increase the physician's index of suspicion that alcohol may be a problem.

- *Blood alcohol level*. The National Council on Alcoholism includes among its criteria for diagnosing alcoholism a blood alcohol level greater than 300 mg/dl at any time or a level greater than 100 mg/dl recorded during a routine clinical examination (41). It also has been noted that a blood alcohol level of more than 150 mg/dl in a patient not obviously intoxicated is strong evidence of significant tolerance to alcohol, and hence potentially of alcoholism. Blood alcohol levels may be obtained either by direct measurement of blood levels or by estimation from the amount of alcohol in expired air using a breathalyzer.
- *Gamma glutamyl transferase* (*GGT*) is an hepatic enzyme that is induced by moderate to heavy alcohol consumption. GGT has been reported to have a sensitivity for detecting heavy alcohol consumption in the 50–70% range (42, 43). Its specificity is in the 75% range (i.e., in 25% of those with elevated GGT, the cause is not due to alcoholism or heavy alcohol intake). GGT in alcoholics returns to normal after approximately 4–5 weeks of abstinence, and it takes about 2 weeks of heavy drinking to acquire abnormal GGT levels (44). GGT levels may also be elevated in patients with hepatobiliary disorders, obesity, diabetes, hypertension, and hypertriglyceridemia.
- *Aspartate aminotransferase (AST)* and *alanine aminotransferase (ALT)*. AST and ALT are increased in liver damage from a variety of causes. AST and ALT have been reported elevated in 30–75% of inpatient alcoholics (31, 45). A ratio of AST to ALT of greater than 2 with ALT values in the 2–8X upper limit of normal range suggest alcoholic hepatitis (46).
- *Carbohydrate deficient transferrin (CDT)* is a relatively new blood test approved by the FDA to screen for heavy alcohol use. Transferrin is involved in the transportation of iron in the body and contains carbohydrate groups on its primary protein. Heavy alcohol use impairs the process of adding carbohydrate groups to transferrin, thus the name carbohydrate deficient transferrin. Elevations in CDT generally occur after the consumption of 60 g of ethanol per day (4–5 standard drinks) for at least 2–3 weeks and persist for 1–2 weeks after sobriety. The advantage of CDT is its greater specificity compared to most other screening tests, e.g. specifity in the 90% range vs. 75% range for GGT. CDT has also been proposed as a tool to monitor treatment outcome as decreases in CDT support reports of sobriety and increases indicate possible relapse to heavy drinking (47).
- *Mean corpuscular volume (MCV)*. Macrocytosis, as indicated by an elevation of the MCV (commonly reported as part of a complete blood count), has been reported to occur in 35–95% of actively drinking alcoholics, with most studies reporting 35–40%. An elevated MCV can also occur in folate and B12 deficiency, hypothyroidism, malignancies, and nonalcoholic liver disease and these causes need to be ruled out. The cause of the elevated MCV in alcoholics is unknown, and it is more marked in alcoholics who smoke. MCV returns to normal 2–4 months after alcohol ingestion ceases (48). Although low in sensitivity this test has been recognized for its low cost and screening value by several studies.
- *Uric acid*. Uric acid levels have been reported to be elevated in heavy drinkers and to return to normal several days after alcohol ingestion ceases (31).
- *Combined GGT/CDT*: A variable derived from the combination of GGT and CDT, the gamma-CDT = 0.8 ln(GGT) + 1.3 ln(CDT), has been shown to enhance discrimination of heavy alcohol use from social drinkers (49). A multinational WHO study (49) reported that this combination was more effective than GGT or CDT in identifying alcohol problems in men but that GGT alone was more accurate in women.

- *Hexosaminidase* serum and urine levels are increased with heavy alcohol consumption and serum levels return to normal after 7–10 days of abstinence and urine levels return to normal after 4 weeks of abstinence (50). Serum hexosaminidase levels can be also elevated in liver disease, diabetes mellitus, hypertension, myocardial infarction, and thyrotoxicosis. Karkkinen et al. (51) reported sensitivities of 69 and 81% for serum and urine hexosaminidase in detecting heavy drinking. The urinary hexosaminidase demonstrated sensitivity of 72% in detecting heavy drinkers after 7 days of abstinence. This was reported to exceed the sensitivity of GGT, ALT, or AST (52).

In summary, a number of laboratory tests can detect heavy drinking with CDT, GGT, and their combination showing the best overall balance of sensitivity and specificity. Efforts to further improve the use of laboratory tests for the identification of heavy drinking and alcoholism are ongoing (43). Functional biomarkers for the acute effects of alcohol on the central nervous system are another important area that is being investigated currently. Clinicians will still need to be educated to utilize laboratory tests for these benefits to be realized.

14.6. Sensitivity and Specificity of Rating Scales for Detecting Alcohol Dependence and Abuse

Self-administered or rater administered questionnaires represent direct screening methods to identify patients with alcohol problems. These questionnaires have been developed to screen populations that are not already identified as having an alcohol problem such as patients in a general hospital, a primary care practice, or a general psychiatric clinic. For the most part alcohol screening questionnaires are greatly underutilized despite the evidence demonstrating their value.

The two questionnaires that have been evaluated the most are the CAGE (53) and the Alcohol Use Disorders Identification Test (AUDIT, (54)). The CAGE is a four item questionnaire (see Table 14.1) and the AUDIT is a ten item questionnaire (see Table 14.2). To reduce the time needed for screening, selected questions of the AUDIT have been evaluated including using just the first three questions (known as the AUDIT-C) or simply using the third question, "Have you had six or more drinks on one occasion in the past year". Overall, the CAGE and the AUDIT have shown acceptable sensitivity (50–90% range) and specificity (70–90%) to detect heavy drinking or alcohol use disorders (55). The AUDIT is better designed to detect heavy and hazardous drinking while the CAGE is better at identifying alcohol abuse and dependence (55, 56). Interestingly, the AUDIT-C and the third question of the AUDIT have shown results nearly comparable to the full AUDIT (57) leading to the suggestion that busy clinicians may wish to simply ask if a patient has consumed six or more drinks on one occasion in the past year in order to identify patients in whom additional inquiries would be of value.

14.7. Clinical Course

Understanding the clinical course of any disease requires longitudinal investigations of individuals with that illness. The clinical course of alcoholism is obscured by a dearth of such longitudinal studies and a lack of agreement on the definition of the illness. The studies that have been done have investigated a subset of patients with alcohol problems, e.g., felons (58), public hospital inpatients (59), private clinic outpatients (60), patients attending various units of a large university hospital or its affiliates (61), married or cohabiting residential treatment inpatients (62), college students (59) and untreated alcohol abusers (63). Despite the limitations of these studies, there are enough of them to provide a reasonable idea of the various clinical courses alcoholism can take.

Historically, the first modern attempt to delineate the course of alcoholism was undertaken by Jellinek (64). He analyzed questionnaires from 2,000 Alcoholics Anonymous members, and from their responses, he postulated that alcoholism is a progressive disease in which 43 distinct symptoms occur in more or less definite order. He grouped the symptoms into three phases:

TABLE 14.1. CAGE questionnaire.

1. Have you ever felt you should *C*ut down on your drinking?
2. Have people *A*nnoyed you by criticizing your drinking?
3. Have you ever felt bad or *G*uilty about your drinking?
4. Have you ever had a drink first thing in the morning to steady your nerves or to get rid of a hangover (*E*ye opener)?

Scoring: Item responses on the CAGE are scored 0 or 1, with a higher score an indication of alcohol problems. A total score of 2 or greater is considered clinically significant.

TABLE 14.2. AUDIT.

Please circle the answer that is correct for you
1. How often do you have a drink containing alcohol? Never Monthly or less 2–4 times a month 2–3 times a week 4 or more times a week
2. How many standard drinks containing alcohol do you have on a typical day when you are drinking? 1 or 2 3 or 4 5 or 6 7–9 10 or more
3. How often do you have six or more drinks on one occasion? Never Less than monthly Monthly Weekly Daily or almost daily
4. During the past year, how often have you found that you were not able to stop drinking once you had started? Never Less than monthly Monthly Weekly Daily or almost daily
5. During the past year, how often have you failed to do what was normally expected of you because of drinking? Never Less than monthly Monthly Weekly Daily or almost daily
6. During the past year, how often have you needed a drink in the morning to get yourself going after a heavy drinking session? Never Less than monthly Monthly Weekly Daily or almost daily
7. During the past year, how often have you had a feeling of guilt or remorse after drinking? Never Less than monthly Monthly Weekly Daily or almost daily
8. During the past year, have you been unable to remember what happened the night before because you had been drinking? Never Less than monthly Monthly Weekly Daily or almost daily
9. Have you or someone else been injured as a result of your drinking? No Yes, but not in the past year Yes, during the past year
10. Has a relative or friend, doctor, or other health worker been concerned about your drinking or suggested you cut down? No Yes, but not in the past year Yes, during the past year

Scoring the audit. Scores for each question range from 0 to 4, with the first response for each question (e.g., never) scoring 0, the second (e.g., less than monthly) scoring 1, the third (e.g., monthly) scoring 2, the fourth (e.g., weekly) scoring 3, and the last response (e.g., Daily or almost daily) scoring 4. For questions 9 and 10, which only have three responses, the scoring is 0, 2, and 4. Reproduced from Saunders JB, Aasland OG, Babor TF, De La Fuente JA, Grant M, Development of the alcohol use disorders identification test (AUDIT): WHO collaborative project on early detection of persons with harmful alcohol consumption-II, Addition 88:791–804, Copyright (1993) with permission from John Wiley and Sons.

prodromal, the first symptom of which is blackouts; crucial, the first symptom of which is loss of control; and chronic, the first symptom of which is binge drinking. In a later work, Jellinek (6) introduced the concept that there are five types of drinking patterns and complications, which he labeled alpha, beta, gamma, delta, and epsilon. He suggested that gamma (characterized by tolerance, craving, and loss of control) and delta (characterized by tolerance, craving, and inability to abstain) represented true diseases that followed most closely his 43 symptoms' progression. In Jellinek's view, once the disease of alcoholism was established, usually when an individual was in his or her early or middle 20s, its course was inexorable, with progression over 20–30 years, ending at any stage in death or abstinence. Many studies then followed, some supporting in part and some seriously questioning Jellinek's conclusions and methodology (65–70).

One of the first studies to challenge Jellinek's hypothesis of an inexorable progression of alcoholism was Lemere's 1953 study (71), in which he asked his patients about the drinking histories of their deceased relatives who had had alcohol problems. He thus collected information on 500 presumed alcohol abusers and found that 28% increased their alcohol use before death; 10% decreased alcohol use substantially, with 3% of the total sample returning to social drinking; 29% did not change their alcohol consumption; approximately 20% stopped drinking because they were too ill to drink; and approximately 10% achieved abstinence. Because of lack of treatment resources available, Lemere concluded that these results, with approximately 20% of those with alcohol problems becoming abstinent or reducing their drinking, represented the natural history of untreated alcoholism.

Vaillant (59) reviewed ten major follow-up studies of alcohol abusers, each of which followed patients for 7 years or longer. The studies had different methodologies and followed different subgroups of alcoholic patients. These studies and others (61, 62), although methodologically disparate, are remarkably similar in indicating that approximately 2–6% of alcoholics remit (are abstinent or drinking in a controlled fashion) each year. These approximations hold for samples of both treated alcoholics [e.g., (59, 72–74)], "skid row" alcoholics (75), and untreated alcoholics (58, 62). Patients in successful remission are about two to three times more likely to be abstinent than drinking in a controlled fashion (59, 62), although one study, which followed socially stable patients, found the reverse (76). The majority of studies have concluded that remitted patients able to drink in a social manner at follow-up were mild cases to begin with (61, 77), although not all studies concur with this conclusion (76). These studies, therefore, partially support Davis's hypothesis that alcoholism is, for some, a self-limiting disorder. However, as is pointed out in studies by Vaillant (59) and Pokorny et al. (78), the more numerous and more severe the symptoms of alcoholism, the closer the clinical picture is to Jellinek's stages and the more alcoholism appears to be a progressive disease, ending in abstinence, serious morbidity, or death. Such conclusions, however, may be tautological; the more serious and numerous the effects (many of which are also symptoms) the more serious the prognosis unless halted by abstinence.

It should be emphasized that the rate of improvement noted earlier applies to patients who are probably diagnosable as being alcohol-dependent. Many patients with alcohol problems, especially those in their teens and 20s, return to social drinking and abstinence at much higher rates. For example, Fillmore (79), in her 20-year follow-up of college students, found that only 30% of 31 individuals who had been problem drinkers in college were still having problems with alcohol at follow-up.

All alcoholics, including those who become abstinent or return to social drinking, are at risk to experience significant medical and psychiatric morbidity from their illness. In addition to the medical and psychiatric complications alcoholics experience, which were noted earlier in this chapter and which frequently lead patients into outpatient or inpatient medical or psychiatric care, alcoholics also experience a great deal of psychosocial morbidity. Given that alcoholism is diagnosed in part by its psychosocial consequences, it is somewhat difficult and arbitrary to separate psychosocial complications from symptoms of alcoholism. It is worth emphasizing, however, that job difficulties and loss; marital tensions, separations, and divorces; and arrests for traffic offenses, disturbing the peace, and criminal behavior are all strongly associated with alcoholism (77).

The various morbidities and traumatic events associated with alcoholism lead to an average age of death of 55–60 years (37). Also of note is the finding of Vaillant (59) that offering intense, readily available treatment to alcoholics does not lower their mortality rate and the finding of Pell and D'Alonzo (80) that the mortality rate of recovered alcoholics is not significantly different from that of alcoholics who continue to drink. Although this latter finding has been supported (62), there are studies that indicate that survival is greater in those alcoholics who are able to abstain or drink moderately than in those who continue as heavy and/or problem drinkers (81–83).

An overall view of the natural history of alcoholism reveals that an alcoholic's first drink occurs at age 13, problem drinking begins between the ages of 18 and 25, first hospitalization for drinking problems occurs at about age 40, and death occurs between the ages of 55 and 60 (37, 77, 84). This natural history differs somewhat for women, who begin problem drinking later than men and have a more rapid development of symptoms (15). Women also have been found to have the onset of physical complications at an earlier age, have more psychiatric disability, have a greater likelihood of co-occurring psychiatric disorders (especially depressive disorder), have a worse prognosis, (especially in relation to mortality), and have an equal response to treatment (37, 40, 85–91).

There are many exceptions to this natural history for both men and women, as there are to the onset, order, and occurrence of specific signs and symptoms of alcoholism. The most severe alcoholic spends much of his or her time sober (40, 92), with

concomitant decreases at such times in alcohol-related problems. The disease appears to fit the pattern of a chronic relapsing illness, with periods of remission and exacerbation. Some alcoholics appear to have permanent remissions either spontaneously, through internal resolve, or with the help of various factors in their environment (93). Others continue a pattern of intermittent but not worsening problems, and still others inexorably deteriorate with increasingly severe, debilitating, and often fatal alcohol-related problems. A continuing challenge to those working in the field of alcoholism is to identify the patients with the more benign course and determine what factors lead to such a course and to identify those with a more malignant course and determine what interventions and treatments are effective for them.

14.8. Differential Diagnosis

Alcoholism has been referred to as a modern day syphilis in the sense that its clinical presentation can take many forms. The medical presentation of the consequences of alcoholism can present as liver disease, cardiac disease, neuropathy, pancreatitis, gastric ulcer, various cancers, infections, traumatic injuries and burns and many other problems. As noted previously, the clinician must be open-minded and willing to entertain the diagnosis of alcoholism as an underlying cause of many clinical presentations. The psychiatric presentation of alcoholism is also often misleading. Because of extensive comorbidity and the shame, ambivalence, and denial in acknowledging one's alcoholism, patients with alcoholism frequently present with complaints and symptoms of depression, anxiety, insomnia, and somatic symptoms. Furthermore, many psychiatric illnesses increase the risk of developing alcohol use disorders and patients with these disorders should be carefully examined for alcoholism. Bipolar disorder has been shown to increase the risk for substance use disorders more than any other Axis I diagnosis (20). It has been shown that 40–50% of hospitalized bipolar patients meet criteria for a comorbid alcohol use disorder (94). Other disorders with high rates of comorbid alcohol problems include antisocial personality, schizophrenia, generalized anxiety disorder, post-traumatic stress disorder, social phobia, attention deficit disorder, bulimia and, to a lesser extent, unipolar depression (20).

Results from the National Epidemiologic Survey on Alcohol and Related Conditions revealed significant comorbidity between alcohol use disorders and drug use disorders (95). Over a 12 month period 7.35% of subjects met criteria for an alcohol use disorder, 0.90% met criteria for a drug use disorder and 1.10% were comorbid for both. Individuals with an alcohol use disorder were much more likely to have a drug use disorder than those without an alcohol use disorder. Individuals with any drug use disorder were 7.4 times as likely to have an alcohol use disorder compared to individuals without a drug use disorder. The presence of comorbid alcohol and drug use disorders increased the likelihood that an individual had sought treatment in the previous year.

14.9. Etiology

There are likely multiple forms of alcoholism and multiple pathways to develop alcoholism. Jellinek (6) was perhaps the first to set forth ideas about subtypes of alcoholism based on his observations of patients over many years. Additionally, a variety of subtypes have been proposed including Type I vs. Type II as described by Cloninger (96), Type A vs. Type B (97), and Lesch's subtyping concepts (98). Type I/II subtypes were derived from behavioral genetic studies using adoptees and clinical populations (96). Type A/B subtypes were derived from cluster analyses applied to a battery of clinical and historical variables gathered on clinical populations (97). Lesch's typology was proposed based on longitudinal observations of alcoholic patients followed over years (98). Though a detailed review of the validity and evidence supporting alcoholism subtypes is beyond the scope of this Chapter, it is noteworthy that some common themes are evident. Most subtypes differentiate alcoholism based on severity of dependence, a greater density of family history of alcoholism, behavioral characteristics such as sociopathy, and comorbid problems such as anxiety and depression. For example, both Type II and Type B alcoholism are characterized by early age of onset, strong family history of alcoholism, heavy alcohol use, and sociopathic behaviors. However Babor and Caetano (99) have recommended that subtyping of alcoholics not be included in formal psychiatric diagnostic criteria until the subtypes are clearly validated in diverse populations.

Identifying the etiology of the alcoholisms is complicated by the fact that there do appear to be multiple forms of the illness. This heterogeneity affects efforts to identify the critical biopsychosocial processes that lead to alcoholism. Nevertheless, our knowledge of the causes of alcoholism has advanced greatly in the past few decades.

The etiology of alcoholism, and its overt expression, involves biopsychosocial factors. Biological factors include genetic risk, phenotypic characteristics, and the impact of environmental events on underlying biology. Psychological factors include variations in personality and temperament, the psychological consequences of stress and trauma, and the impact of other mental illnesses. Social factors include cultural influences, the current social milieu, and regulatory policies such as current laws, taxation, health warnings, and limits on advertising.

14.9.1. Biological Influences

14.9.1.1. Genetics

Alcoholism runs in families. This observation was noted thousands of years ago by Plutarch "One drunkard begets another" (100). About four times as many children of alcoholics become alcoholic as do children of nonalcoholics. For years, it was unclear whether this increased rate was a familial effect or represented true genetic risk. Over the past 40 years a number of adoption and twin studies have been completed that unequivocally demonstrate a strong genetic component to alcoholism. The first series of studies were adoption studies in Denmark (101), Sweden (102), and the United States (103). Each of these studies found that the adopted away children of alcoholic parents were significantly more likely to develop alcoholism than the adopted away children of nonalcoholic parents. The Swedish study also indicated that subtypes of alcoholics may vary in the extent of genetic risk. Thus, the Type II alcoholic (more severe form of illness) was found to have a robust genetic influence independent of environmental influence whereas the Type I alcoholic showed evidence for a gene–environment interaction (104).

Twin studies complement adoption studies and have provided a powerful tool for the study of genetic factors in psychiatric disorders. Twin studies are based on the fact that monozygotic (MZ) twins share 100% of their DNA whereas dizygotic (DZ) twins, similar to any sibling, share 50% of their DNA. Therefore, disorders in which genes contribute to etiology should exhibit greater concordance in MZ twins than in DZ twins. Studies in MZ vs. DZ twins using various definitions of alcoholism have revealed strong evidence for a genetic component. This has been demonstrated in both male (105) and female (106) twin pairs. Examination of the contribution of environmental and genetic influences on the development of alcoholism in these studies leads to estimates that genes contribute on the order of 50–60% to etiology. One important point from twin studies is that the development of alcoholism is not inevitable, even if one inherits genetic risk—concordance rates are not 100% for MZ twins. Alcoholism is neither a dominant nor recessive Mendelian trait. Therefore, the inheritance of risk for alcoholism appears to involve multiple genes interacting in a probabilistic manner to increase risk—some individuals are at very high risk and others are below average risk.

14.9.1.1.1. Search for the Genes Underlying Alcoholism

Major efforts have been undertaken over the past 20 years to identify genes that increase or decrease risk for alcoholism. These efforts have been greatly advanced by the rapidly expanding knowledge of the human genome and the development of techniques to identify genes for complex diseases.

Probably the first series of genes to attract interest were those that code for the enzymes involved in alcohol metabolism. Alcohol (ethanol) is initially metabolized by alcohol dehydrogenase to acetaldehyde which is then metabolized by aldehyde dehydrogenase to acetic acid. Variants in either of these enzymes have been shown to affect risk for alcoholism and for alcohol-related pathology such as esophageal cancer (107, 108). When ethanol is rapidly converted to acetaldehyde and/or when acetaldehyde breakdown is reduced, the level of acetaldehyde reaches relatively high levels after alcohol consumption. Acetaldehyde is a noxious metabolite and can produce nausea, dizziness, sweating, rapid heartbeat, low blood pressure, headache, and flushing. This is the same reaction as the disulfiram reaction and is a deterrent to consumption. Therefore if one inherits a slow metabolizing form of aldehyde dehydrogenase, consumption of alcohol will lead to aversive effects and a reduced likelihood of drinking. In fact, it has been repeatedly documented that individuals with the slow metabolizing form of acetaldehyde have very low rates of alcohol dependence (109). These variants are most common in some Asian populations and less common in individuals from a Caucasian or African background.

Genes not involved in the metabolism of alcohol must contribute to those biological forces that promote consumption, loss of control, and compulsive use. Many studies have been published reporting one gene or another to be associated with alcoholism but relatively few have been well replicated. Several associations that have been replicated include genes for the alpha2 subunit of the GABA-A receptor and the cholinergic muscurinic 2 receptor (110) and variants of the dopamine 2 receptor (111). Other identified genes include the gamma-3 subunit of the GABA-A receptor, the kappa 1 opioid receptor and its endogenous ligand prodynorphin, and the TAS2R16 bitter taste receptor (110). These discoveries are building the framework from which to begin to understand the genetic-biological basis of the various types of alcoholism. It will be important to link the genetic findings to phenotypic expressions, e.g., anxious vs. nonanxious, disinhibited vs. inhibited, to draw a more complete picture of the alcoholisms with greater relevance to clinicians and implications for treatment.

14.9.1.2. Phenotypic Risk Factors

The phenotypic expression of risk for alcoholism takes many forms. There is no single high-risk phenotype. Two of the best replicated phenotypes that, in multiple studies, predict risk for alcoholism are: (1) low-level of response to alcohol (LR) (112) and (2) neurophysiological disinhibition (113). LR takes the form of reduced motor impairment and less subjective sense of

intoxication following an alcohol challenge and has been observed in young social drinkers with family histories of alcoholism. Prospective study of these individuals has shown that LR in the early years of drinking is significantly associated with overt alcohol abuse and dependence later in life (112). Efforts are now underway to identify the genetic basis of LR and preliminary findings indicate associations to variations in the serotonin transporter promoter and the GABA-A receptor alpha-6 subunit (114).

Neurophysiological disinhibition has been extensively studied as a risk factor for alcoholism. Begleiter and colleagues were the first to identify a reduced P300 potential in response to an odd-ball task as a potential marker of risk for alcoholism (115). Since then a broader theory of cognitive and behavioral disinhibition as a risk phenotype has emerged (113) and genetic associations to this phenotype have been reported as well (116). One intriguing observation is that this phenotype appears to be associated with conduct disorder and sociopathy which, as noted above, are found in Type II/Type B alcoholics (see Sect. 14.9).

Other phenotypes associated with risk for alcoholism have been reported, e.g. trait anxiety, beta-endorphin response to alcohol, and it is possible that tens or even hundreds of phenotypes will eventually be identified. A great deal of work remains to identify those phenotypes that can be easily assessed by a clinician and shown to have practical diagnostic, prognostic, or therapeutic value.

14.9.1.3. Neurobiology, Neuroadaptation, and Disease Progression

One of the underlying tenets of the etiology of substance use disorders is the critical role played by the endogenous reinforcement system (117). Alcohol, similar to other drugs of abuse such as cocaine or opiates, activates mesolimbic and mesocortical dopamine neurons leading to an acute reinforcing effect (positive reinforcement). Whereas this rewarding effect is important, recent research in neurobiology reveals that, over time, neuroadaptational processes emerge that are equally, if not more important, in the maintenance of alcohol intake and the development of compulsive use patterns (117). Furthermore, recent evidence indicates the development of negative behavioral consequences, e.g. heightened stress sensitivity, decreased hedonic responsivity, anxiety, with chronic consumption of alcohol that are likely important for driving relapse (negative reinforcement) (25, 118). In patients, these neuroadaptations may take the form of a protracted withdrawal syndrome with stress intolerance, insomnia, anxiety, and dysphoria, all of which can contribute to relapse.

14.9.2. Psychological Factors

An addictive personality was part of clinical parlance 30–40 years ago. Assessment instruments were developed, e.g. the McAndrew Scale derived from the MMPI, to identify the addictive personality. However, a unitary "addictive personality" has not been confirmed. Rather, many different personality/temperament types, e.g. antisocial personality features, anxiety traits, and a temperament of behavioral undercontrol, are at risk for alcoholism.

Early life physical and sexual abuse have also been identified as important factors in the development of alcohol use and other substance use disorders in women though their effects may be mediated through psychiatric illnesses (119).

14.9.2.1. Role of Primary Psychiatric Illnesses in the Development of Alcohol Use Disorders

Primary psychiatric illness is a significant factor in the development of alcohol problems. As noted above, a variety of psychiatric illnesses increase the relative risk of having an alcohol use disorder. The highest risk occurs with bipolar disorder, schizophrenia, and antisocial personality. Anxiety disorders including generalized anxiety disorder, social phobia, and post-traumatic stress disorder increase risk for alcohol use disorders as does attention deficit disorder and depression. Unipolar depression only slightly increases risk.

14.9.3. Cultural Factors

The expression of alcoholism requires access to alcohol. Therefore, factors that reduce access such as cultural prohibitions, legal restrictions, and cost, including taxation, all can affect the prevalence of use. Furthermore, cultural norms and pressures can affect drinking related behavior. An excellent example of the latter is the dramatic reduction in alcohol-related traffic deaths that have occurred over the past 20 years following a variety of public policy steps including increased public awareness and stricter legal sanctions (120).

14.10. Treatment

14.10.1. Treatment of Alcohol Withdrawal

The treatment of alcoholism and the management of alcohol withdrawal symptoms present separate problems.

In the absence of serious medical complications, the alcohol withdrawal syndrome is usually transient and self-limiting; the patient recovers within several days regardless of treatment (121). Symptoms of alcohol withdrawal usually begin in the first 12–24 hours after consumption has ceased. Symptoms include activation of the sympathetic nervous system with increased blood pressure and heart rate, sweating, and tremor; nausea, vomiting, headache, restlessness, agitation, anxiety, insomnia, and paranoia; disturbances in tactile, auditory or visual perception which may include dramatic hallucinations though rarely of "pink elephants". Grand mal seizures represent one of the serious consequences of alcohol withdrawal. Alcohol withdrawal seizures usually occur within the first 48 hours after drinking has stopped. Delirium tremens (DTs) is a serious consequence of alcohol withdrawal with a mortality rate in the 5–10% range. DTs are characterized by (1) delirium with disorientation and waxing and waning of consciousness and (2) severe autonomic activation including tremor, tachycardia, increased blood pressure, profound diaphoresis and fever. DTs peak 48–96 hours after drinking has stopped. Probably less than 5% of alcoholics experience serious withdrawal upon stopping alcohol. However, as referred to earlier, a protracted withdrawal syndrome may persist for months to a year or longer and likely contributes to risk for relapse.

The ability to predict which patients will have a serious withdrawal syndrome would be of great clinical value. These patients would require inpatient hospitalization and detoxification while low-risk patients could be monitored on an outpatient basis. Not surprisingly, there are no definitive predictors for serious withdrawal. Rather, a number of factors have been identified that increase the relative risk of having serious withdrawal complications including delirium tremens or a seizure. Factors that increase risk include comorbid medical illness such as acute infections, fractures, or burns, prior history of DTs or a seizure, longer time before treatment starts, increased severity of typical alcohol withdrawal symptoms including systolic blood pressure >145 mm Hg or heart rate >120 (122–126). It is recommended that patients having one or more of these risk factors receive medical detoxification. The Clinical Institute Withdrawal Assessment for Alcohol Revised [CIWA-Ar, (127)] has emerged as the most common assessment instrument to monitor the severity of alcohol withdrawal. The most widely used version consists of ten questions assessing nausea, headache, tremor, sweating, anxiety, agitation, auditory disturbances, tactile disturbances, visual disturbances, and orientation. CIWA-Ar scores greater than ten or so in the first 24 hours after cessation of alcohol indicate that medication treatment could be helpful; scores greater than 15 (124) indicate an increased risk for serious withdrawal problems.

Treatment of withdrawal is generally highly effective—the mortality rate from alcohol withdrawal has been greatly reduced over the past 60 years but not to zero. The benzodiazepines are considered the drugs of choice for withdrawal (128, 129) with solid evidence that they reduce the risk of DTs and seizures. The benzodiazepines are a diverse group of medications that vary across a number of parameters including: (1) half-life; (2) hepatic metabolism, (3) rapidity of onset; (4) availability of IV and IM parenteral formulations. Lorazepam is commonly used in acute medical settings because it is not metabolized by the liver, has a short half-life allowing more rapid control, and can be given parenterally. Conversely, long-acting agents such as chlordiazepoxide or clorazepate, are more commonly used in psychiatric settings. Barbiturates are effective treatments for alcohol withdrawal but their use has declined because of their narrow toxic/therapeutic index compared to the benzodiazepines. For agitation, paranoia, hallucinations, and aggression that do not respond to early intervention with benzodiazepines, antipsychotic medication, particularly haloperidol, has been shown to have clinical value though clear risks as well (129).

Administration of thiamin and other B vitamins is obligatory in the treatment of alcohol withdrawal. Thiamin deficiency is known to contribute to Wernicke–Korsakoff syndrome and its administration can prevent the irreversible memory deficits seen in Korsakoff's. Thiamin is poorly absorbed from the gastrointestinal tract in alcoholism therefore IM or IV doses of adequate amount, e.g. 100 mg, for several days is recommended.

Unless the patient is dehydrated because of vomiting or diarrhea, there is no reason to administer fluids parenterally. Contrary to common belief, alcoholics usually are not dehydrated; actually, they may be overhydrated from consumption of large volumes of fluid (130).

If the patient develops delirium, he or she should be considered dangerous to himself or herself and others, and protective measures should be taken. Ordinarily, tranquilizers calm the patient sufficiently to control agitation, and restraints are unnecessary. Most important, if delirium occurs, further exploration should be conducted to rule out serious medical illness missed in the original examination. When a patient is delirious, an attendant should always be present. It is sometimes helpful to have a friend or relative present.

14.10.2. Post-Detoxification Treatment

It has been said that the treatment of alcoholism begins once acute alcohol withdrawal is over. Of course, not all patients will complete a medical withdrawal and treatment can begin before alcohol consumption stops. Treatment has multiple goals though the key goal is to help the alcoholic maintain sobriety and reduce the impact of relapses. O'Brien and McLellan (131) have persuasively argued for viewing alcoholism as a chronic illness similar to hypertension or diabetes mellitus. Thus, alcoholism requires ongoing management and is characterized by variations in course from long-term sobriety to episodic relapses to progressive deterioration despite treatment.

The biopsychosocial nature of alcoholism has led to the development of biopsychosocial interventions. Traditionally, psychosocial interventions have been most prominent but, recently, biological interventions are gaining more interest as efficacy is demonstrated.

The primary treatment goal for the alcoholic patient is long-term sobriety. A reduction in harmful drinking can be an appropriate goal, particularly in order to maintain a therapeutic relationship with a patient who is not motivated for abstinence. A goal of reduced consumption as a *primary* outcome is more controversial though this has been utilized with some success, particularly in patients with less severe dependence (132).

Because alcohol use disorders are heterogeneous and exhibit a wide range of severity, treatment is equally diverse. Thus, the heavy drinking patient without clear alcohol dependence may respond to brief interventions in a primary care setting (133) whereas the seriously dependent individual with multiple alcohol-related consequences will likely need detoxification and residential care in a specialized program.

When broaching the issue of an alcohol problem to a patient it is useful to have some sense of what the patient's reaction will be. Patients present differently in their readiness to accept the diagnosis of alcohol dependence/ abuse and in their readiness to change. Prochaska and DiClemente (134) have developed a theoretical model for understanding how patients change behavior derived from studies of smoking cessation. The model has five stages: (1) precontemplation; (2) contemplation; (3) preparation; (4) action; (5) maintenance. Precontemplation identifies those patients who are not ready to hear that they have an alcohol problem—it simply is not in their awareness. The goal with these patients is to maintain a therapeutic relationship and, over time, to help them accept that alcohol is causing them problems. Confrontation with these patients may simply lead to a rupture of the therapeutic relationship. Fortunately, many patients can move beyond precontemplation and begin to take steps to change their drinking behavior and come to terms with the role alcohol plays in their life. For these patients a variety of treatment approaches are available.

14.10.2.1. Psychosocial Interventions

Many psychosocial treatments have been tried for alcoholism, from psychoanalysis to cognitive-behavioral therapy to aversive therapy. A comprehensive review of psychosocial interventions for alcoholism is beyond the scope of this chapter. An excellent critical and comparative review of psychosocial treatments that have been studied in clinical trials is provided by Miller and Wilbourne (135). Based on evidence of efficacy, they find that brief interventions, social skills training, community reinforcement approaches, behavior contracting, behavioral marital therapy, and case management show the best efficacy. Least supported are methods designed to educate, confront, shock, or foster insight regarding the nature and causes of alcoholism. What is not clear from the existing literature is what kind of treatment should be utilized for a given alcoholic patient. For example, it would be predicted that a severely dependent patient will benefit more from an intense course of treatment than a brief intervention, though this has not been carefully tested in clinical trials.

Brief interventions are of interest to the nonspecialist clinician because they can be implemented in a general medical setting. Fleming et al. (133), in a randomized, controlled study, found that two brief interventions of 10–15 minutes of counseling, feedback, and a personal contract conducted by general physicians to heavy drinkers led to significant reductions in binge drinking and excessive drinking after 12 months. Importantly, four year follow-up revealed that the patients who had received the intervention continued to have reductions in drinking behaviors as well as fewer days of hospitalization, fewer ED visits, and an overall savings of $43,000 in health care costs for every $10,000 invested in the intervention (136). These findings reinforce the importance of identifying problem drinking in the primary care setting and highlight that noncomplex behavioral interventions can produce significant clinical improvements. It should be noted that the patients in this study were not formally diagnosed with alcohol dependence or in need of medical detoxification.

In contrast to the above findings, a recent meta-analysis of studies of SBI (screening and brief intervention) in primary care settings did not show significant reductions in subsequent health care utilization (137). The efficacy of SBI in other settings, such as emergency departments (EDs) or hospitals, has not been established, although several randomized controlled trials have been conducted (138).

Attempts to predict which psychosocial treatments work best with which alcohol dependent patients have generally not found clear superiority for one treatment over another based on patient characteristics. The largest such trial to date was Project MATCH (139). This randomized trial gathered a wide range of assessments, e.g., drinking patterns, psychiatric symptoms, on 1,726 alcoholic subjects who entered the study following residential treatment (aftercare) or as outpatients. Subjects were randomly assigned to one of three treatments provided over 12 weeks: Cognitive Behavioral Coping Skills Therapy (12 sessions); Motivational Enhancement Therapy (4 sessions); or Twelve-Step Facilitation Therapy (12 sessions). Subjects were evaluated at 1 year and then at 3 years. Overall, outcomes were very good with 35% of aftercare subjects and 19% of outpatient subjects continuously abstinent for 12 months. Furthermore, 60% of aftercare subjects and 54% of outpatient subjects did not experience three consecutive days of heavy drinking during this time. Follow-up at 3 years revealed that 30% of patients were abstinent for the final 3 month evaluation and those who did report drinking were still abstinent an average of two-thirds of the time (140). Each of the three interventions was effective but the hypothesis that subgroups of alcoholic patients would respond preferentially to one of the treatments was not demonstrated.

14.10.2.2. Alcoholics Anonymous and Other Self-Help Groups

Alcoholics Anonymous (AA) has been widely viewed as providing more help for alcoholics than any other approach. AA was started in the 1930s by two alcoholics, Bill W. and Dr. Bob, and the interested reader is referred to any number of historical accounts to learn more. Key elements of AA include the acknowledgement that one is powerless over alcohol (Step 1), a fellowship of recovering alcoholics who meet regularly, and the acceptance of a belief in a power higher than oneself. The full 12 steps of AA provide a framework that many individuals report has led to long-term sobriety and a positive transformation in their lives. AA estimates that there are currently about 1.1 million AA members in the United States in about 52,000 groups. Their 2004 membership survey reports 65% of members are men and that 36% report sobriety for more than 10 years and 26% report sobriety for less than 1 year. AA discourages research or formal relationships with medical institutions so a controlled clinical trial of AA has not been completed. Studies have been completed of interventions designed to facilitate AA attendance, including the Twelve Step Facilitation program designed for Project MATCH, and these have shown efficacy (139). However, probably no more than 5% of alcoholic individuals are active in AA.

There is no question that AA provides help for many alcoholics that they cannot obtain elsewhere. No doubt it has saved many lives. Most clinicians who treat alcoholics commonly encourage their patients to attend AA meetings. It is not possible to predict in advance whether one patient will benefit from AA and another will not. AA just about everyone agrees should be given a fair opportunity.

Clinicians should also consider referring family members of the alcoholic to Alanon or Alateen. These self-help groups are designed for the families of an alcoholic individual with awareness that the family needs support regardless of whether the alcoholic is in treatment. As family members become educated about alcoholism they can feel empowered and, sometimes, help the alcoholic to enter treatment.

There are aspects of AA that lead some individuals to avoid it. One key issue is the role of the "higher power" or "God as we understood Him". A significant number of individuals interpret this as an endorsement of a form of religion and find this off-putting. Partly in reaction to this, other self-help groups have emerged including rational recovery and Smart Recovery. These programs utilize techniques similar to cognitive-behavioral therapy and do not call upon a "higher power."

Women for Sobriety is another self-help program that differs from AA and was founded to address the needs of women seeking recovery. Women meet in groups for support and are encouraged to reflect daily on 13 affirmations such as "I have a life-threatening problem that once had me". Many women attend both AA counseling and Women for Sobriety.

Clinicians should be aware of these alternative self-help programs and whether they are available in their area. Several online counseling service, treatment programs, and interactive websites are offered currently for individuals who are unable to access traditional treatment programs or who want to strengthen their recovery after a traditional program. Their impact has yet to be studied. Online apps have also shown some promise as another strategy for self-help but these also need to be systematically studied.

14.10.2.3. Medication Treatment

The use of medications to treat alcoholism entered a new phase in 1995 with the FDA approval of naltrexone. Prior to that the only FDA approved medication for alcoholism was disulfiram (Antabuse®).

14.10.2.3.1. Disulfiram

Disulfiram is an alcohol-sensitizing aversive treatment that was discovered serendipitously in the 1940s. Disulfiram irreversibly inhibits aldehyde dehydrogenase leading to a buildup of acetaldehyde when ethanol is consumed. Acetaldehyde produces a number of aversive symptoms including headache, weakness, dizziness, flushing, rapid heartbeat, low blood pressure, nausea, and sweating. This experience can be severe and, in vulnerable individuals, several fatalities have been reported (141). Deaths from disulfiram have not been reported in recent years probably because of the use of lower doses and the exclusion of patients with cardiovascular disease (142). Disulfiram treatment of alcoholism is therefore based on two principal actions—a psychological deterrent to use because of the threat of a reaction and a physiological deterrent to use because of the overt reaction if alcohol is consumed.

Early reports based on case series were quite positive. Case series can be misleading and with the development of modern clinical trial methodology, randomized, placebo-controlled trials of disulfiram were completed. However, even these trials were complicated by the fact that a significant component of the disulfiram effect is provided by the knowledge that one is taking the drug. Therefore, a placebo disulfiram can accomplish this same action. The largest controlled trial of disulfiram was a VA study of 605 subjects (143). In that study, 250 mg of disulfiram was blindly compared to a 1 mg disulfiram dose and an open vitamin condition was provided to control for counseling. Subjects were followed for 1 year. No differences were detected between medication assignment and rates of complete abstinence. Compliance with treatment was strongly related to abstinence. However, in subjects who relapsed to drinking and in whom assessment was complete, those randomized to disulfiram had significantly fewer drinking days. Additional work has noted the value of supervised administration with disulfiram (144), such as by a spouse or treatment center. Overall, the evidence suggests that disulfiram has value in the treatment of alcoholism (145). Clearly, patients must be motivated to take disulfiram, preferably under some form of supervised use. Patients need to be warned about exposure to other sources of alcohol in mouthwash, cologne, and foods. They also need to be aware that the disulfiram effect can last up to 2 weeks after disulfiram is stopped while aldehyde dehydrogenase is resynthesized.

14.10.2.3.2. Naltrexone

Naltrexone is a nonspecific opioid antagonist that blocks μ, δ, and κ opioid receptors. Based on the knowledge that part of alcohol's reinforcing effects are mediated through brain opioid systems, clinical trials of naltrexone were completed in the early 1990s. These early trials (146, 147) revealed that 50 mg of naltrexone reduced the risk of relapse to heavy drinking compared to placebo by about half. Effects on abstinence were not as robust. Since these initial reports, naltrexone has been studied in about 3,000 subjects in placebo-controlled trials throughout the world. Meta-analyses reveal that the strongest effect of naltrexone is to reduce the risk of relapse to heavy drinking (5 or more drinks on one occasion for a man and 4 or more drinks for a woman) with marginal effects on abstinence (148–150). Reductions in drinking frequency and drinks/drinking days have also been reported. A number of studies have shown that naltrexone reduces the "high" experienced from alcohol if a lapse occurs (151). Other reports have noted a reduction in self-reported craving for alcohol with naltrexone but reductions in craving are not the primary goal with naltrexone,

Naltrexone is usually started after several days of abstinence to reduce side effects and advance the patient's treatment goals. Patients who are abusing opiates or require opiates for pain management should not receive naltrexone. Naltrexone has been reported to cause liver problems when given in higher doses and the physician should probably not use naltrexone in patients with acute alcoholic hepatitis. Patients should probably remain on naltrexone at least 6–12 months and quite possibly longer depending on response and risk for relapse.

14.10.2.3.3. Acamprosate

Acamprosate is structurally related to gamma-amino-butyric acid but its mechanism of action has been proposed to be a reduction in alcohol-induced glutamatergic hyperactivity—a factor possibly contributing to protracted withdrawal (152). Clinical trials with acamprosate in over 4,000 subjects have generally been very consistent and reveal that acamprosate increases the likelihood of complete abstinence about two fold. In patients who do not maintain complete abstinence acamprosate increases the number of abstinent days (148). The majority of acamprosate trials have been completed outside the United States in settings where patients have established abstinence. The two clinical trials completed in the United States recruited many non-treatment-seeking patients who had shorter periods of abstinence and both of these trials were negative (153, 154). Mason et al. (153) did note a positive effect of acamprosate on days abstinent in subjects who had a goal of abstinence.

Acamprosate is well tolerated by most patients with mild diarrhea being the primary side effect. Acamprosate is usually started once a patient has achieved abstinence. The dose is 666 mg orally three times per day. No titration is needed. How long to continue acamprosate is not clearly defined but many clinicians would advocate continuation for 1 year or so to allow the patient to solidify behavioral changes.

14.10.2.3.4. Long-Acting Naltrexone

The development of long-acting formulations of naltrexone was a goal originally envisioned for the treatment of opiate addiction. A long-acting formulation has the advantage of ensuring a steady delivery of medication even in a patient who is ambivalent about taking medication and has compliance problems. The discovery that naltrexone is effective for alcoholism has led to a number of trials with long-acting naltrexone (LA-NTX) in patients with alcohol dependence (155, 156). Both of these studies used formulations that were administered intramuscularly at monthly intervals. The Garbutt et al. (155) study used a dose of 380 mg/month and found a main effect for LA-NTX in reducing heavy drinking by about 50% over a six month trial length. Subjects who were abstinent prior to injection demonstrated the greatest responses and, in these subjects, LA-NTX significantly increased the likelihood of complete abstinence. Kranzler et al. (156), using a different formulation and an initial dose of 300 mg followed by two monthly doses of 150 mg, did not find a significant effect on the primary outcome measure of number of nonheavy drinking days, though a number of secondary outcome measures, including complete abstinence, were significantly improved with LA-NTX. In both of these trials LA-NTX was well tolerated. A concern that long-lasting opiate blockade might present a clinical problem in case opiate medications were needed was not realized. Nevertheless, clinicians need to be aware of this potential issue. Clinical experience with LA-NTX is just beginning and it will be important to gauge its effectiveness in the general clinical setting. The availability of a long-acting medication for alcoholism with demonstrated efficacy is a new and valuable addition to treatment.

14.10.2.3.5. Combinations of Medications

It is clear that for most behavioral disorders combinations of medications sometimes work better than monotherapy. To that end, a variety of medication combinations have been tried in alcoholism. Two trials have examined the efficacy of acamprosate + naltrexone compared to each monotherapy and to placebo. The evidence is mixed. One German study (157) found evidence for superiority of the combination compared to acamprosate or placebo but not to naltrexone. Acamprosate and naltrexone monotherapy were each superior to placebo. A trial in the United States (154) did not find evidence for improved outcomes with the combination but also failed to find a main effect for acamprosate whereas one was found for naltrexone. Naltrexone and acamprosate have also been tried with disulfiram in nonrandomized studies and the combinations appear tolerable though proof of added efficacy remains questionable.

Clinically, based on current evidence, most patients should be offered treatment with either acamprosate, naltrexone, or LA-NTX and then monitored. Some patients may be good candidates for disulfiram. Patients who cannot tolerate one agent should be offered another. In cases where outcomes are less than satisfactory, consideration should be given to combining acamprosate and naltrexone/LA-NTX.

14.10.2.3.6. New Directions

Nalmafene is a newer opioid receptor modulator. It acts as an opioid antagonist at mu and delta receptors and as an agonist at kappa receptors. It has been reported to be safe and effective in a recent 24 week double-blind placebo-controlled trial for treatment of patients with alcohol dependence (158). Six hundred and four alcohol dependent patients were recruited. Half of them were assigned to the active intervention group, the other half received placebo. Patients were instructed to take one tablet on each day they felt they could relapse. Patients who received Nalmafene showed decreased alcohol consumption and their medical status improved with improvement in their hepatic function tests (158). Nalmafene was well tolerated and side effects were mild to moderate and resolved quickly (158). This study shows promise but further research is indicated. Nalmefene is currently approved in Europe.

Although not FDA approved topiramate, which resembles acamprosate in its mechanism of action, was reported to be better than placebo in controlling drinking over a period of 14 weeks (159).

14.10.2.3.7. Pharmacogenetics

An emerging area of science is the identification of genetic polymorphisms that predict treatment response to specific pharmacotherapies. Given the evidence that alcoholism is heterogeneous and that multiple genes are involved in the etiology of alcoholism it would be predicted that genetic variants would preferentially respond to specific pharmacotherapies. However, this area of investigation is very much in its infancy and, so far, no findings have emerged that can be readily translated to the clinic. In a preliminary study, Oslin et al. (160) reported that patients who carried the Asp40 allele for the μ-opioid receptor had better responses to naltrexone than patients who were homozygous for the Asn40 allele. This finding is of interest but needs confirmation. Genetic screening will likely be used by clinicians at some point to help choose a medication for alcoholism.

14.10.3. Overall Effectiveness of Treatment for Alcoholism

O'Brien and McLellan (131) noted that one of the myths about the treatment of addiction is that treatment is not effective. In fact, they presented evidence that the treatment of the addictions, including alcoholism, is probably as effective as the treatment of other chronic medical disorders such as diabetes or hypertension. Furthermore, much depends on the definition of what is successful treatment for the alcoholic. Certainly, long-term abstinence is the primary treatment goal for the alcohol dependent patient but the majority of patients will relapse one or more times after treatment. Should these patients be considered to have failed treatment? O'Brien and McLellan (131) argue no, they should not be considered failures. Other outcomes, including substantial reductions in heavy drinking, should be considered positive in their own right and as way stages on the road to long-term sobriety (161).

The question still arises, how effective is treatment for alcoholism? It is helpful to have a sense of this to be able to inform patients and their families that treatment is effective. To answer this question, Miller et al. (162) examined seven large multisite studies that systematically tracked outcomes. One year after treatment about 25% of patients remained continuously abstinent and another 10% used alcohol moderately and without problems. The remaining 65%, overall, greatly reduced their alcohol use and had significantly fewer alcohol problems. Rates of abstinence and reductions in drinking quantity and frequency will, of course, vary from treatment program to treatment program depending on many factors. Furthermore, some patients will not enter treatment. Nevertheless, the key point noted by Miller et al. (162) and by O'Brien and McLellan (131) is that treatment is effective for many patients and far too many patients never receive treatment.

14.11. Concluding Comment

The understanding of alcoholism as a biopsychosocial disease has changed dramatically since the time of Rush and Trotter in the 1780s and even since the founding of AA in the 1930s. We now know that there is, indeed, a strong genetic factor in alcoholism. We understand at a much finer level of detail the neurobiological and medical consequences that alcohol produces overtime and how these contribute to the progression of the disease. We know that public policy can reduce the deadly consequences of heavy alcohol use given sufficient political will. Yet, our relationship with alcohol remains complex, ambivalent, and conflicted. The majority of adults in the United States consume alcohol. Alcohol is visible at celebrations, in our cities, on our college campuses, and in our media. Physicians all too often avoid discussing the use of alcohol in talking with patients and do not recognize the warning signs of unhealthy alcohol use (163).

Hopefully, one of the next cycles in our relationship with alcohol will be to meld our increasing knowledge of the science of alcohol with a greater awareness and motivation to help the millions of individuals and their families who struggle with the destructive side of alcohol, this "water of life" [(2), pg. 11].

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15
Drug Addiction

Joseph Westermeyer, M.D., M.P.H., Ph.D. and Gihyun Yoon, M.D.

Abstract Drug addiction, a chronic relapsing disorder, causes an enormous burden to patients, families, and societies. This chapter summarizes current concepts of drug addiction, epidemiology, etiology, pathogenesis, pathology, clinical course, laboratory findings, assessment, and treatment on drug addiction. Pathologic consequences from drugs of abuse (e.g., opioids, sedatives, amphetamines, cocaine, cannabis, tobacco, phencyclidine, hallucinogens) are explained as well. The understanding of drug addiction has improved by recent progress in genetics, neuroscience, pharmacology, and psychiatry. It is now possible to treat drug addiction more effectively using advanced psychological and pharmacological interventions.

Keywords Addiction · Drugs of abuse · Behaviors · Course · Treatment

15.1. Definition

Drug addiction is a major health problem that leads to enormous morbidity and mortality. More evidence, especially from animal and neuroimaging studies, has demonstrated that drug addiction is a chronic brain disease, not just a character problem (1, 2), although it can affect personality, moral decisions, and behavior in adverse ways. Repeated drug use causes brain changes in addicted patients, who tend to relapse easily in the context of environmental cues, cravings, or stress. Despite significant negative consequences, drug-dependent patients are often unable to cease their drug use without treatment. Addictive disorders tend to vary widely over time and in various communities, so that environmental factors play a larger role in addictions as compared to many other psychiatric disorders.

Criteria for drug addiction have undergone changes in the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) (3). DSM-5 describes drug addiction as a "substance use disorder (SUD)" that combines the former DSM-IV diagnoses of substance abuse and substance dependence. DSM-5 has added drug craving as one of the 11 criteria of SUD, while eliminating legal problems from the criteria (for a detailed list of 11 criteria, please consult DSM-5).

Physiochemical properties of drugs weigh into the diagnosis, but clinical judgment still must be applied regardless of drug dosage. For example, mixed drug abuse, mental retardation, dementia, other psychiatric conditions, comorbid medical conditions, and extreme youth or advanced age may lead to drug-related problems at doses lower than usual. Even relatively mild psychoactive compounds, such as caffeine or tobacco, can lead to disabling symptoms in vulnerable patients or in large doses. Episodes of opioid or cocaine overdose, amphetamine delusional disorder, phencyclidine delirium, or cannabis delusional disorder exemplify other types of pathologic drug use.

J. Westermeyer, M.D., M.P.H., Ph.D. (✉)
Professor, Department of Psychiatry, University of Minnesota School of Medicine, Staff Psychiatrist, Addictive Disorders Service, Mental Health Service, Minneapolis VA Medical Center, Minneapolis, MN, USA
e-mail: weste010@umn.edu

G. Yoon, M.D.
Assistant Professor of Psychiatry, University of Minnesota, Staff Psychiatrist, Addictive Disorder Team, Mental Health Service, Minneapolis VA Medical Center, Minneapolis, MN, USA
e-mail: yoonx033@umn.edu

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Physiological dependence involves the presence of tolerance to the drug or withdrawal upon stopping use. With tolerance, the patient must consume markedly increased amounts of the drug to achieve the desired effect, or there is markedly diminished effect with regular use of the same amount. Sudden drug withdrawal results in abstinence symptoms if tolerance is present. Different drugs produce withdrawal symptoms as follows:

Opioids: Lacrimation, rhinorrhea, mydriasis, piloerection, sweating, abdominal cramps, diarrhea, yawning, anxiety, irritability, mild hypertension, tachycardia, fever, or insomnia.
Sedatives: Nausea, vomiting, malaise, weakness, tachycardia, sweating, hypertension, anxiety, depressed mood or irritability, orthostatic hypotension, coarse tremor, and possible disorientation, hallucinations, or convulsions in severe cases.

Stimulants: Fatigue, disturbed sleep, headache, craving, unpleasant dreaming, or increased appetite.
Tobacco: Craving, irritability, anxiety, depression, or difficulty concentrating.
Cannabis: Anxiety, restlessness, anger, insomnia, decreased appetite, depressed mood, abdominal pain, tremors, headache, sweating, fever, or chills.
Caffeine: Sleepiness, fatigue, difficulty concentrating, depressed mood, or headache.

Onset of abstinence symptoms following the last dose varies with the drug's duration of action, as well as the drug's half-life (the amount of time for half of the drug to be metabolized and inactivated within the body). Withdrawal can begin in 2–6 hours with short-acting drugs (e.g., lorazepam, heroin, morphine, tobacco), in 8–24 hours with intermediate-acting drugs or those with increasing half-lives (e.g., opium, phenobarbital), or in days to weeks with long-acting drugs or those whose half-life has increased with repeated administration of dependence-producing doses (e.g., buprenorphine, ethchlorvynol, diazepam, methadone).

Cannabis withdrawal is included in the DSM-5 (3). Chronic heavy cannabis users experience a need for markedly increased doses to achieve the desired effect and/or markedly diminished effect from regular doses. Lack of clinically significant abstinence symptoms may be due to storage of active cannabis fractions (e.g., tetrahydrocannabinol) in body fat stores, with gradual excretion over days or weeks. In patients with cannabis-related psychosis, symptoms may not abate until these fat stores are depleted of cannabis.

DSM-5 includes tobacco use disorder, which is characterized by tobacco withdrawal syndrome, unsuccessful attempts to stop or reduce its use, or continued use despite a serious tobacco-related physical disorder (e.g., emphysema, coronary artery disease, Berger's arterial disease).

Drugs can induce mental disorders such as delirium, dementia, amnestic disorder, psychosis, mood disorder, anxiety, sexual dysfunction, or sleep disorder. Other drug-related conditions include hallucinogen-induced hallucinosis, hallucinogen or cannabis delusional disorder, and hallucinogen-induced mood disorder. Substance-related amnestic disorder and mood disorder may accompany drug use. Depending on duration and pattern of drug use, these diagnoses may or may not be accompanied by drug addiction.

15.2. Etiology and Pathogenesis

Excessive or problematic drug use and its final common pathways within the brain (i.e., nucleus accumbens, ventral tegmentum, and the frontal lobes) comprise the behavioral and neurophysiological mechanisms for drug addiction. However, numerous risk factors drive these mechanisms so that drug addiction is generally conceived as being multifactorial in its etiology. The public health model of agent (drug), host (drug-using individual), and environment (family, friends, community, society) has proven useful in conceptualizing the complex causes of drug addiction.

15.2.1. Host Factors

15.2.1.1. Genetic Influences

Like many other psychiatric disorders, drug addiction is highly heritable. Genetic components of addiction liability range from 39% for hallucinogens to 72% for cocaine (4). Heritability portions of addiction liability range from 40% to 70% for other drugs, such as stimulants, cannabis, sedatives, tobacco, alcohol, and opioids. One family study reported an eightfold increased risk of substance disorders in relatives of probands with substance use disorders (5). Twin and adoption studies have also demonstrated that substance disorders are correlated with genetic and environmental factors (6, 7). Offspring of heavy tobacco smokers are considerably more apt to become tobacco dependent than the general population (8). Opium-dependent persons show a higher rate of opium dependence among their siblings and relatives than does the general population. Similarly, drug-dependent persons in the United States often have alcoholic relatives, as well as depressed or manic relatives (6).

Several genes contribute to the vulnerability to addictions. The genetic variants of the following genes have been reported to induce addiction vulnerability: the μ-opioid receptor (OPRM-1) gene for alcoholism and heroin addiction (9); catechol-O-methyltransferase (COMT) for heroin, stimulant, tobacco, and alcohol dependence (10); dopamine D4 receptor (DRD4) for

alcohol, heroin, and stimulant addiction (11); serotonin transporter gene (SERT, SLC6A4) for alcohol, tobacco, and heroin addiction (12); and nicotine acetylcholine receptor gene (CHRNB3, CHRNA6) in tobacco addiction (13).

15.2.1.2. Neurobiological Variables

Repeated drug use changes the neurobiological system of the individual addicted to drugs of abuse. In 1954 Olds and Milner reported that rats would stimulate their brain endlessly via implanted electrodes in the pleasure center (14). This center is now known as the reward circuit encompassing the ventral tegmental area (VTA) to the nucleus accumbens. Various drugs of abuse increase dopamine—the "pleasure molecule"—in the reward circuit (15). Dopamine released in this pathway leads to positive reinforcement. Chronic drug use causes neuroadaptations and plasticity (e.g., changes in synapses, gene expression) in the host's brain including the reward circuit. Other areas involved in drug addictions are the prefrontal cortex (e.g., orbitofrontal cortex, anterior cingulate), lateral basal amygdala, and extended amygdala (e.g., nucleus of stria terminalis, central medial amygdala) (16). In the initial stage of addiction, individuals tend to use drugs of abuse to increase positive reinforcement (increasing addictive behaviors to receive pleasure and rewards), but their behaviors become compulsive mainly due to negative reinforcement (increasing addictive behaviors to remove the aversive states) in the later stage of addiction (17).

15.2.1.3. Psychological Variables

Psychological and personality traits usually accompany drug addiction, although it is difficult to ascertain the extent to which these are etiologic or secondary to drug abuse. Factors that initially lead a person to start drug use may change over time so that the original causes may be replaced by different or altered factors that drive continued or increased drug use (18). No one personality type predates drug abuse, although those with chronic pain, anxiety, depression, mania, psychosis, inattention, hyperactivity, impulsiveness, and/or antisocial attitudes appear to be at greater risk. Personality characteristics of drug abusers, perhaps as much acquired as primary, typically include hostile dependence on others, low frustration tolerance, limited flexibility and adaptiveness, low self-esteem, risk taking, and novelty seeking (19).

Several theories regarding host psychology, difficult to test in either laboratory or clinical settings, remain popular but still unproven. The "anxiety reduction theory" states that some people take drugs initially to reduce tension, especially in social settings (20). The "state-dependent theory" holds that drug abusers rely more on internal rather than external cues in making decisions and adjusting to life and thus are vulnerable to exogenous drug administration as a means of modifying internal states (21). The "career-addict hypothesis" suggests that many drug-dependent persons cease their drug-taking career later in life as they "mature out" of drug use (22, 23).

15.2.2. Agent Factors

15.2.2.1. Pharmacology of Drugs of Abuse

Drugs differ in their acute toxicity, chronic toxicity, and relative risk of addiction. For example, addiction liability is highest for cocaine and amphetamine, high for opioids and tobacco, medium for alcohol and benzodiazepines, lower for cannabis, and lowest for hallucinogens (24).

Pharmacologic properties of drugs themselves affect their propensity for abuse. Opioids and sedatives produce rapid, albeit temporary, relief of anxiety, fear, and insomnia. Stimulants relieve boredom, somnolence, low energy, and fatigue. Drugs that alter perceptions or impede memory may aid in blocking out distressing thoughts or feelings. Symptoms relieved by drugs of abuse include pain, hunger, sexual dysfunction, nausea, vomiting, cramps, diarrhea, and cough.

Drugs with more rapid onset of action (e.g., heroin, alprazolam) tend to be preferred for abusive purposes over more delayed-onset drugs (e.g., methadone, clonazepam). Modes of administration with liability for drug abuse include intravenous injecting, smoking, and snuffing, which produce quicker drug effect (several seconds) than subcutaneous injection or ingestion (20 minutes or more).

Tolerance and withdrawal phenomena also contribute to drug abuse syndromes. Tolerance, the need for increasing doses to produce the same effect, is particularly characteristic of opioids and sedatives but also occurs with stimulants, cannabis, and tobacco. As addicted persons consume larger doses to achieve the dwindling target effects due to tolerance, minimal or no tolerance may develop to other unintended effects that become worse with increasing doses (e.g., constipation and sexual dysfunction with opioids, hypertension, and vascular spasm with cocaine). Cessation of drug use in the tolerant individual precipitates withdrawal, a morbid state that persists hours, days, to weeks (depending on the drug) in its acute phase. Subclinical abstinence symptoms can continue for months in the second phase of withdrawal. These subacute abnormalities, best described for opioid

drugs and alcohol, consist of altered sleep patterns, vital signs, and endocrine functions, which may persist for up to a year. Anxiety symptoms, panic attacks, irritability, suspiciousness, low pain tolerance, depressive symptoms, and sometimes manic symptoms may persist for weeks. Sedative or opioid withdrawal produces weakness, anorexia, tachycardia, agitation, insomnia, irritability, social withdrawal, and remorse. Stimulant withdrawal causes fatigue, hyperphagia, bradycardia, and somnolence. In the chronic stages of substance use disorders, drug usage may continue more to avoid withdrawal than to achieve intoxication.

15.2.2.2. Host–Agent and Environment–Agent Considerations

Host factors may interact with drug factors in various ways. Insomniac, anxious, rageful, or chronic pain patients may seek relief of their symptoms in opioids and sedatives. Bored, fatigued, or depressed individuals may pursue liveliness from stimulant drugs. Those seeking a pharmacologic "time out" from their ordinary cognitions may enjoy the effect of hallucinogens.

As availability of a drug increases in the environment, its prevalence increases (22). Distance between sales outlets, hours of sale, and restrictions on sale to minors governs availability of licit substances. Prohibition of a substance usually leads to decreased availability, but this is not inevitably true. Availability of prescribed drugs can be due largely to prescribing habits among physicians. The greatly increased use of benzodiazepines in the late 1960s and 1970s, and their waning use in the 1980s, hinged largely on physician prescribing practices. Amphetamine prescribing, prevalent during the 1950s to 1970s, also declined. The opioid epidemic now raging in the United States and parts of Europe has resulted from overly casual prescribing by licensed prescribers, lax monitoring by clinicians, and the heavy time-and-resource challenge needed for clinicians to address iatrogenic addiction compared with simply filling another opioid prescription (25).

Cost of drugs of abuse influences their use. As price increases, drug use tends to decrease, even if availability is held constant. This is one argument for drug prohibition laws, which often increase the cost of drugs considerably (since they are illicit) but may not greatly reduce availability for those who cannot afford them.

15.2.3. Environmental or Social Factors

15.2.3.1. Social Traditions Regarding Drugs of Abuse

Cultures that effectively prohibit or preferentially ignore certain drugs have little or no problems with them. For example, alcohol abuse is rare in certain Muslim nations that forbid alcoholic beverage for religious reasons. However, sanctions against one substance do not necessarily prohibit use of other drugs. For example, certain Middle Eastern countries have high rates of opioid dependence.

Patterns of use for a particular drug determine the likelihood that the drug will be associated with abuse. Non-ritual use away from family, in a surreptitious fashion, with intoxication as a goal tends to be pathogenic. Safe use occurs primarily when everyone in the society is introduced to the drug experience in a family-sponsored, multigenerational, socially approved, or sacred setting, with ritual feasting and celebration. Peyote use in the Native American Church comprises an example (26).

Only one or a few drugs can be thus woven into the fabric of a society. Families cannot enculturate their offspring into all drugs to which they may be exposed. Cultures generally approve a few mild intoxicants (e.g., tobacco, caffeine, betel–areca) and perhaps a few stronger intoxicants (e.g., alcohol, peyote) but not the more addicting or potentially psychopathologic drugs (e.g., heroin, amphetamine, phencyclidine). Recent state laws permitting cannabis use have shown an increase in use (as one would predict from societal support of use), but problematic use shows early indications of increasing (e.g., more cannabis-related accidents, crime, and health consequences) (27).

15.2.3.2. Drug Laws

Anti-drug laws began to appear several hundred years ago. Prior to 1500 AD, the Aztecs strictly controlled alcohol use by dose, frequency, and social status (28). Asian and European kingdoms enacted laws regarding tobacco and opium in the 1600s AD. Anti-drug legislation accelerated in the eighteenth to twentieth centuries. We are still in the era of worldwide drug diffusion, as modified drugs (e.g., cocaine from coca, heroin from opium), new manufactured drugs (e.g., synthetic opioids, sedatives, stimulants, hallucinogens), and new methods of administration (e.g., skin patches, sublingual preparations) spread from one part of the world to another.

Regulations prohibiting drug use have been most effective in countries with strong centralized power, including both rightist and leftist police states. They have been weakest in democratic and socialist countries that rely heavily on citizen support for compliance. Legislation alone, without other social interventions in education, health, commercial, religious, and ethnic sectors, can exacerbate drug problems by driving drug production, distribution, and use into a criminal subculture (29).

15.3. Epidemiology

15.3.1. Methods of Study

Epidemiologic assessment is key in measuring the extent of drug abuse, in planning interventions, and in observing the results of treatment and prevention efforts over time. Self-report, blood and urine tests, withdrawal signs, and autopsy studies have been used as measures. Sampling methods have ranged from door-to-door surveys to studies of special populations (e.g., students, medical patients, arrested persons in jail).

One special technique used for drug abuse epidemiology is the capture–recapture technique, a method drawn from measuring the number of fish, birds, or other animals in a free-ranging population. In this method, a number of individuals are first "captured," then released, and subsequently "recaptured." For example, the number of diagnosed addicts "captured" in a particular subgroup is measured (e.g., those admitted to a treatment program, say, 100 over a period of time). Then the number of drug abuse cases "recaptured" or surfacing to another group is measured (e.g., deaths in a morgue or arrests by the police, again over a specified period of time). If, say, 1 person out of ten arrested addicts is known to have previously received care at the treatment facility and 100 addicts previously treated at the facility are arrested, then the capture–recapture method would suggest that 1,000 drug abuse persons lived in the community.

Another special method has been the registry, most often used for opioid abusers. One central agency collects data on opioid abusers admitted for treatment or rehabilitation, seeking help at social agencies, arrested, convicted for opioid possession, or dying from an opioid-related cause. Complications used to track drug abuse have included antibodies against serum hepatitis, overdose deaths from opioids and sedatives, and sudden death in association with cocaine use.

The assumptions behind any of these methods may be flawed, leading to estimated rates higher or lower than the true rate. For this reason more than one estimator should be employed. Even if an estimator is flawed, it may be flawed in a consistent way over time, permitting the observation of rate trends over time. For example, mortality from hepatic cirrhosis or drug overdose can reflect age- and gender-related rate changes over time, without necessarily revealing the true prevalence of drug addiction in the population.

15.3.2. Rates of Substance Use Disorder

Prevalence of lifetime and past-year drug use disorder (excluding alcohol or tobacco) is 10.3% and 2.0% in the United States (30). For alcohol use disorder, lifetime and past-year prevalences are 30.3% and 8.5% (31). For tobacco dependence, lifetime and past-year prevalence are 24% (32) and 12.8% (33).

Rates of drug abuse often fluctuate widely over time and from place to place. Several opioid and amphetamine "epidemics" have occurred over the last century. Tobacco dependence increased progressively over the last century among men and more recently among women, although rates among men in the United States have been declining. Cannabis use increased markedly during the late 1960s but has declined somewhat since then while still being widely used. Cocaine use disorder has fluctuated up and down several times from the 1970s until now. Pharmacists annually fill tens of millions of prescriptions for benzodiazepines, with a relatively small but persisting level of abuse. Combined use of opioids with either benzodiazepines or additional secondary opioids has contributed to the greatly increased mortality associated with prescribed opioids (34).

15.3.3. Demographic Characteristics

Men generally engage in drug abuse more frequently than women, although there are exceptions. Betel nut chewing in parts of Asia and prescription sedative abuse in North America and Europe have occurred predominantly among women. In recent years, the rates of tobacco, alcohol, and iatrogenic opioid dependence have been increasing more among American women than men.

Since World War II, drug abuse has begun to affect teenagers to a considerable extent, although it formerly began primarily in adulthood. Elderly people have shown increased rates of alcohol and sedative abuse, often in association with retirement, death of a marital partner, isolation from friends and family in residences for the elderly, major depression, chronic pain, or disabling medical conditions (35).

Socioeconomic variables affect the availability and type of drugs. For example, successful drug smugglers, athletes, and entertainers have had both the money for and access to such drugs as cocaine and heroin. Because of the low rate of drug interdiction by law enforcement officers, students have been able to afford cannabis and other drugs.

Medical workers are especially liable to abuse prescription drugs. Of 10 substance-abusing physicians, 1 is usually abusing drugs only. The remaining 9 are abusing alcohol primarily while often abusing other drugs to offset the effects of alcohol. Drug-dependent physicians have preferred the synthetic opioids in recent years, perhaps because these drugs have been incorrectly touted as less addicting than the opium-based drugs (e.g., morphine). Nurses, pharmacists, and dentists show similar patterns. Some health professionals have abused illicit or "street" drugs, including cannabis and cocaine.

15.4. Pathology

Pathologic consequences from drug abuse vary widely with the drug, dosage, duration of use, and route of administration. In order to provide safe treatment, the clinician must be able to discern intoxication, withdrawal, and overdose for the main drug categories. See Table 15.1 for the symptoms associated with these conditions. Intoxication and overdose tend to exist along a spectrum, with "mild-to-moderate" intoxication being the goal of the typical drug user, but with "severe overdose" posing morbid or even mortal consequences for the patient. For any given drug category, intoxication and withdrawal tend to present as polar opposites of one another due mainly to their neurotransmitter manifestations.

Depending on how much drug the patient has taken, and when, the clinical picture may change dramatically over time. A patient who has not absorbed all of the consumed drug into the blood may progress from intoxication to overdose in the clinical setting. Or a substance-dependent patient may proceed from intoxication into withdrawal.

Depending on the drug, these various clinical stages may be more or less dangerous. With some drugs, some patients, and some clinical conditions, observation over a period of hours or a few days may be the treatment of choice. With other drugs and patients, timely action may be needed to stave off highly morbid or even mortal conditions. If medication is needed, the general rule is an agonist for withdrawal and an antagonist for overdose.

15.4.1. Opioids

Although opioid drugs differ considerably in dosage (see Table 15.2) and duration of action, the maximal potencies of the stronger opioid drugs (e.g., morphine, heroin, fentanyl, methadone) are quite similar. Weaker opioids (e.g., codeine, propoxyphene) cannot equal them, even in large doses. Some opioids, such as pentazocine and buprenorphine, have mixed agonist-antagonist effects, so that increasing the dose or adding it to another opioid drug can precipitate withdrawal symptoms.

Regarding methadone, equivalent doses in Table 15.2 apply only if the patient is not physiologically dependent on the opioid drug. In the presence of tolerance, equivalence between methadone and other opioids cannot be readily determined for two reasons. First, the half-life of methadone lengthens once the dose increases above 20 mg per day, and especially above 40 mg per day. Second, the duration of the increasing half-life and the peak blood level of methadone can differ considerably from one person to the next even after stable doses have been achieved. For both of these reasons, the risk to overdose fatality is great, especially in the hands of clinicians unfamiliar with transitions between other drugs and methadone. A safe transition procedure includes the following steps: administer between 5 and 15 mg doses and then observe the patient for several hours before repeating doses; do not administer more than 30 mg on day one even in a patient with tolerance; and increase by small increments over subsequent days (3–5 mg increments every 3 days).

Buprenorphine is not included in Table 15.2 for three reasons. First, starting buprenorphine in some patients who have another opioid in the nervous system can precipitate withdrawal. Second, like methadone, the half-life of buprenorphine begins to increase beyond 4 mg per day, so that it has no simple equivalence to other opioids above that dose. Third, considerable individual variation in metabolism occurs, so that some individuals may attain atypically low or high blood levels (36).

There are three types of opioid receptors: μ, δ, and κ. Neuroimaging and animal studies have demonstrated that the reinforcing effects and opioid addiction are mediated and modulated mostly by μ-opioid receptor.

Opioids can relieve pain, anxiety, cough, and diarrhea. Especially in the naive user, they produce nausea and vomiting. While early use may relieve social and sexual inhibition, chronic use leads paradoxically to social withdrawal and decreased libido. Tolerance to analgesia begins with the first dose, so opioids are excellent for acute, severe pain but less effective for chronic or recurrent pain.

Acute effects include meiosis or pinpoint pupils (which occur with most but not all opioids), constipation, urinary hesitancy, hypotension, and lethargy. Coma and possibly death by respiratory depression can result from overdose. Arrhythmias, heart block, or death may also result from a prolonged QT duration of the heart rhythm, especially in those with familial prolongation of the QT, older age, and concomitant treatment with other medications prolonging the QT interval. The withdrawal syndrome, beginning 4–36 hours after the last dose (depending on the opioid drug and dose), consists of agitation, piloerection, dilated pupils, muscle aches, and abdominal cramps with elevated pulse, blood pressure, and temperature. A subclinical withdrawal syndrome consisting of sleep disturbance, irritability, vital sign fluctuations, and autonomic nervous system lability may persist for several months in tolerant individuals (37).

TABLE 15.1. Drug signs.

	Intoxication						Overdose						Withdrawal			
	ALCOHOL	**STIMULANTS**	**SEDATIVES**	**OPIOIDS**	**HALLUCINOGENS**	**PHENCYCLIDINE**	**ALCOHOL**	**STIMULANTS**	**SEDATIVES**	**OPIOIDS**	**HALLUCINOGENS**	**PHENCYCLIDINE**	**ALCOHOL**	**STIMULANTS**	**SEDATIVES**	**OPIOIDS**
Vital Signs																
Circulatory collapse							•		•	•	•		•		•	•
Hypertension		•				•		•			•	•	•		•	
Hyperthermia		•			•			•			•		•		•	
Orthostatic hypotension							•		•	•			•		•	•
Respiration, slow and shallow							•		•	•						
Tachycardia		•			•	•	•	•			•	•	•		•	•
Appearance, Behavior, and Mental Status																
Affect, labile	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
Comprehension, slow	•		•	•	•	•	•		•	•	•	•	•	•	•	
Delirium	•	•	•			•	•	•	•	•	•	•	•		•	
Delusions	•	•	•	•		•	•	•	•	•	•	•	•		•	
Depressed mood	•		•				•		•				•	•	•	•
Euphoria	•	•	•	•	•	•										
Hostile, assaultive	•	•	•			•		•			•	•	•		•	•
Irritability	•	•	•			•		•			•	•	•		•	•
Lethargy	•		•	•			•		•	•				•		
Memory, poor	•		•	•		•	•		•	•			•		•	•
Restlessness		•			•	•	•	•	•	•	•	•	•		•	•
Skin picking		•		•				•					•		•	
Suspiciousness		•			•	•		•			•	•	•	•	•	
Sweating								•					•		•	•
Talkativeness	•	•	•	•				•								
Vomiting	•			•		•	•	•	•	•	•	•	•		•	•
Yawning			•													•
Eyes, Ears, Nose, and Throat																
Coryza																•
Lacrimation																
Mouth, dry		•			•			•			•					
Nystagmus	•		•			•	•		•			•	•			
Pupils, dilated		•					•	•	•	•	•					•
Pupils, pinpoint				•						•						
Rhinorrhea														•		
Neurological Examination																
Analgesia to pinprick	•		•	•		•	•	•	•	•		•				
Coma							•		•	•		•				
Convulsions			•				•	•	•	•	•	•	•	•		•
Dysmetria	•		•	•		•	•		•	•		•				
Facial grimacing						•		•								
Hypotonia	•		•	•			•		•	•	•			•		
Muscle spasms (rigidity)						•		•				•	•		•	•
Reflexes, hyperactive		•				•		·			•	•	•		•	•
Speech, slurred	•		•	•		•	•		•	•		•				
Stare, blank	•		•	•	•	•	•	•	•	•	•	•				
Tremor	•	•	•					•			•		•		•	•
Skin																
Flushing	•			•	•		•	•		•	•		•		•	
Piloerection (gooseflesh)																•

Adapted with permission from Westermeyer J: Primer on Chemical Dependency: A Clinical Guide to Alcohol and Drug Problems. Baltimore, Williams & Wilkins, 1976.

TABLE 15.2. Dose equivalents of opioid drugs in patients without opioid dependence.

Drug	Dose equivalent (mg)		Dosing interval (hours)
	Oral	Parenteral	
Morphine	30	10	3–4
Codeine	130	75	3–4
Diamorphine	12.5	5	3–4
Fentanyl	NA[a]	0.1	1–2
Hydromorphone	4–6	1.5	3–4
Hydrocodone	60	NA	3–4
Meperidine	150–250	75	3
Methadone	10	5	3–4
Oxycodone	20	15	3–4

[a]*NA* not available (50 mcg/hour patch).

TABLE 15.3. Dose equivalents of benzodiazepines in patients without sedative dependence.

Drug		Dose equivalent (mg)	Half-life (hours)
Generic	Trade		
Alprazolam	Xanax	0.25	12
Chlordiazepoxide	Librium	10	100
Clonazepam	Klonopin	0.5	34
Diazepam	Valium	5	100
Lorazepam	Ativan	1	16
Midazolam	Versed	1.5	3
Oxazepam	Serax	15	8
Temazepam	Restoril	5	11
Triazolam	Halcion	0.1	2

15.4.2. Sedatives

These drugs include the benzodiazepines, barbiturates, glutethimide, methaqualone, chloral hydrate, paraldehyde, and ethchlorvynol. Although showing cross-tolerance with alcohol, they are synthetic and chemically dissimilar to each other. Sedatives with rapid onset of action tend to be abused more readily. Longer-acting sedatives produce a more stable withdrawal regimen.

See Table 15.3 for equivalent doses of the sedatives. The half-lives depicted are averages; the spectrum ranges considerably lower to higher for these medications. Note the long half-lives of diazepam and chlordiazepoxide—two effective medications for treatment of sedative or alcohol withdrawal. The use of shorter-acting benzodiazepines produces a stormy withdrawal course, with patients alternating between agitation and delirium as blood levels wane, with lethargy to stupor when levels are high.

Benzodiazepines and barbiturates act on the ionotropic γ-aminobutyric acid (GABA) type A receptor. When substances are attached to GABA receptor, GABA opens the chloride channel to render the cell less excitable. Sedative drugs are more apt to be abused by those presenting to physicians with symptoms of insomnia, palpitations, tachycardia, headache, epigastric burning, or similar psychophysiologic symptoms of anxiety. Much sedative abuse in the United States has an iatrogenic component. Careful psychiatric assessment and monitored prescribing reduce sedative abuse.

Duration of action and margin of safety differ widely among the sedatives. Like the opioids and alcohol, they can produce tolerance if taken chronically in increasing doses. Acute effects include incoordination, dysarthria, lethargy, and somnolence; overdose leads to coma and death by respiratory depression. Prolonged QT duration with heart block and sudden death can occur with some sedatives, such as the benzodiazepines, in vulnerable persons. The withdrawal syndrome consists variably of tachycardia, fever, hypertension, headache, agitation, and tremor. Seizures, confusion, delusions, and hallucinations occur in severe cases. Onset of withdrawal can occur within several hours after the last dose of short-acting sedatives or within several days to weeks with the long-acting sedatives (38).

15.4.3. Amphetamines and Similar Drugs

These drugs (including methylphenidate) are often abused by night workers, those doing prolonged repetitive work requiring alertness (e.g., truck driving), or chronically dysthymic individuals. Amphetamines facilitate the release of two neurotransmitters: (1) dopamine from presynaptic vesicles, thereby increasing the robust reinforcement effects, and (2) norepinephrine,

thereby increasing pulse, blood pressure, metabolic rate, and sometimes temperature. Stimulant effects on the central nervous system include mydriasis, tachycardia, elevated mood, heightened self-confidence, alertness, dry red skin, and wakefulness with a decrease in rapid-eye-movement (REM) sleep.

Tolerance and increased daily doses occur in chronic users. Confusion, panic, and paranoia may ensue, and a psychotic state similar to schizophrenia or mania can persist for days, weeks, or months. Hyperthermia, hypertension, arrhythmias, convulsions, and cerebrovascular accidents accompany overdose. Withdrawal consists of lethargy and increased REM sleep. Depression, which often appears following withdrawal, may be a withdrawal effect, a sign of an emerging primary depression, or some combination of both (37).

15.4.4. Cocaine

Like amphetamines, cocaine abuse is apt to ensue in the user who is bored, fatigued, or depressed. Since the intoxicant effect is extremely short compared with other drugs of abuse, the user may snort, smoke, or inject drugs several times an hour to sustain the drug effect. Under such circumstances, the cost of a cocaine habit can mount readily. The heavy user may become financially destitute or enter an illegal occupation (e.g., drug smuggling or selling, burglary, prostitution) to obtain the drug (39). Despite cocaine's brief duration of action, its metabolite benzoylecgonine remains detectible in urine for a few days following use.

One form of cocaine is the hydrochloride form, taken by injection or snorting. The paste form, used for smoking, involves an extraction from coca leaves using a dangerous combination of kerosene and sulfuric acid. Cocaine potentiates catecholamine effect by interfering with reuptake of dopamine, norepinephrine, and serotonin at their transporter sites. Its effects are similar to those of amphetamine but with a half-life persisting over minutes rather than hours. Certain complications resemble those of amphetamine use, such as paranoia, hallucinations, or hypertension.

15.4.5. Cannabis

Although numerous psychoactive compounds exist in cannabis, most of its effect appears to be due to delta-9-tetrahydrocannabinal. Cannabinoids bind to the cannabinoid receptors. Potency of cannabis preparation varies with proximity of the farming site to the equator, climate, plant species, part of the plant consumed, and procedures to increase potency (e.g., hashish). Consumed by eating or smoking, its effect persists for a few to several hours, depending on dose, tolerance, and pattern of use.

Many people seem able to consume small amounts of cannabis at infrequent intervals (i.e., weekly or monthly) without ill effect. Vulnerable individuals may experience hallucinations, delusions, or confusion at low doses. With chronic, heavy use, the percentage of impaired users probably increases.

Intoxication involves aspects of both stimulation and depression, sympathetic and parasympathetic manifestations (40). These include dry mouth, increased appetite, tachycardia, injected conjunctivae, and relaxation. Coordination for simple tasks is not impaired at lower doses, although balance, estimation of time, and complex tasks become increasingly impeded with higher doses. Minutes may be perceived as hours. This may contribute to the enhanced sexual enjoyment reported by some or the impaired speed estimation and distance measurement causing vehicular accidents (41). Short-term memory loss leads to disjointed thinking, with consequent silliness, social withdrawal, or panic.

Some tolerance occurs with chronic use. The cannabis withdrawal syndrome includes anxiety, irritability, chills, sweats, malaise, insomnia, decreased appetite, and craving. Since tetrahydrocannabinol is stored in fat, chronic users may excrete the drug for days or even weeks following the last use.

15.4.6. Tobacco

Whether consumed by smoking, snuffing, or chewing, tobacco's psychoactive effect is largely due to nicotine. Like cocaine, the half-life of nicotine is brief (under an hour). Many carcinogens (e.g., tar) exist in tobacco. Nicotine, which mimics the effects of acetylcholine, acts as a mild stimulant. Nicotine mediates the reward effect and addiction by increasing dopamine in the reward circuit. Although smoking produces almost instantaneous effect, absorption after oral ingestion is slow. Chewing produces an intermediate onset. Effects include increased heart rate, gastric atony, and peripheral vasoconstriction. Large doses may produce nausea, emesis, and convulsions. One cigarette ingested by a small child can be lethal. Withdrawal effects include bradycardia, irritability, and increased appetite.

Heavy smokers maintain plasma nicotine levels by smoking tobacco about every half hour. Tobacco consumption in dependent persons may be linked to such biologic events as waking up, eating, and bowel movements. Smoking also reinforces

activities (e.g., meeting with friends, sexual encounters). If the nicotine content in a cigarette is decreased, dependent smokers adjust by increasing their inhalations.

As a mild intoxicant with few or mild effects on cognition, mood, and coordination, tobacco rarely produces acute problems. However, it can produce numerous, sometimes catastrophic, damage to health, including heart disease, emphysema, Berger's disease, and lung cancer. Health complications increase markedly after 20 pack-years of smoking (i.e., one pack per day, per year, over 20 years). Although tobacco dependence is notoriously difficult to reverse permanently, nicotine withdrawal or replacement pharmacotherapy, bupropion, varenicline, motivational enhancement, cognitive-behavioral approaches, and physician recommendations to cease tobacco use are effective (42). During tobacco cessation, weight gain is a frequent complication.

15.4.7. Caffeine

In lower doses of 50–150 mg, caffeine reduces fatigue and enhances mental activity while causing some tachycardia, vasodilatation, and diuresis. It produces these effects by stimulating catecholamine release. Higher doses (i.e., over 600 mg per day) may produce excitement, agitation, headache, irritability, and insomnia. Withdrawal symptoms in high-dose users (i.e., over 1,000–1,200 mg per day) can include fatigue and somnolence (43).

Caffeine is present in many common beverages, including coffee (120–150 mg per cup), tea (50–80 mg per cup), cocoa, colas (50–70 mg), and other soft drinks. It also occurs in many over-the-counter and prescription drugs taken for pain, appetite suppression, and the common cold. Excessive caffeine use can cause dependence, manifested by withdrawal (i.e., headache, fatigue, craving) and tolerance (44).

15.4.8. Volatile Hydrocarbons

These substances have acute psychotoxic effects similar to alcohol, but with a shorter half-life, often under an hour. Effects include ataxia, dysarthria, elation, and silliness. Special populations such as prisoners, industrial workers, or children sniff them, since they are available, inexpensive, and short acting. Aerosols, glue, cleaning and industrial solvents, and paint thinners can produce hepatic, renal, hematologic, or neurologic damage depending on the chemical, pattern of use, and individual propensity (45). Early symptoms of chronic use, which may come to the attention of a pediatrician or psychiatrist, are irritability, declining academic or occupational performance, memory loss, and personality change. Amyl nitrate use for sexual enhancement has led to chronic abuse (46). Endemic and epidemic use has prevailed among children over the last several decades. Originally reported in American Indian and Hispanic communities, it has spread to other communities.

15.4.9. Phencyclidine (PCP)

PCP functions as an antagonist at the *N*-methyl-D-aspartate (NMDA) subtype of glutamate receptors. This versatile drug may be ingested, snuffed, smoked, or injected. Its effects are variable, so it may produce relaxation or panic, hypotension or hypertension, decreased reflexes, or status epilepticus. In general, however, it potentiates adrenergic effects. Impurities from illicit production may cause anticholinergic effects. Body-image distortions, agitation, and hallucinations are common in PCP users coming to clinical attention. Vertical or horizontal nystagmus, muscular rigidity, and dystonic reactions are clues to the diagnosis. Half-life is relatively short but after-effects can continue over hours or a few days due to enterohepatic recirculation. Acute and chronic users may present to emergency rooms with various psychiatric syndromes from panic attack, to mania, to psychosis, and to delirium (47).

15.4.10. Hallucinogens

These include natural substances (e.g., peyote, morning glory seeds) and synthetic compounds (e.g., n-lysergic acid, or LSD). LSD functions as a partial agonist at the serotonin type 2 (5-HT2) receptor. Altered perceptual states are produced; panic, hallucinations, and delusions may occur. While the half-lives of these drugs are only a few hours, psychic effects may persist for 6–12 hours. Hallucinosis can continue for a few to several days in unusual cases. Vulnerable individuals can experience first episodes or recurrences of mania, psychosis, delusional disorder, or schizophrenia. Physical manifestations are few, except for possible anticholinergic toxicity with dry warm skin, increased pulse, urinary hesitancy, and memory disturbance (47). Accidental poisoning can precipitate a psychiatric emergency, with hallucinations and panic.

15.5. Clinical Picture

15.5.1. The Great Imitator

The clinical picture depends on the drug, duration of abuse, route of administration, the individual's nutritional status, associated medical and psychiatric problems, and socioeconomic impairment. Impairment may be minimal, with early or mild signs or symptoms, or so severe that signs and symptoms irrefutably support the diagnosis. Patients may hide, alter, or accurately describe their drug use and its associated problems, depending on their openness, wish for help, and extent of discomfort. A key factor is the clinician's comfort and skill in aiding patients to relate their history. A nonjudgmental attitude toward patients is critical. Clinical skill as well as judgment in managing drug abuse cases requires supervised clinical training. Without training and experience, the clinician is not likely to perceive the clinical picture accurately nor to manage the case in a supportive and therapeutic fashion.

Substance abuse has been called the "great imitator" of our time for good reason. It may present with medical, psychiatric, or surgical pictures. Drug abusers are found in medical settings more frequently than expected from their number in the population. Drug-related problems are proportionately more common among inpatients than among outpatients. Patients may present quite early in their course or in severely advanced stages. The problem may be acute or chronic, life threatening or minor, readily discerned or vague, and difficult to define. See Table 15.4 for psychological manifestations during early, middle, and late stages of addiction.

15.5.2. Data Collection

Substance use disorders tend to be progressive, beginning with an early phase and advancing into middle and late phases; see Table 15.5. Substance-related behavior comprises a core aspect of these changes over time, but other behaviors also show changes (e.g., grooming, control, reliability, conversation). The rapidity at which these phases progress varies with the type of drug, the individual, and the environment. The entire course may telescope down to a few years or may proceed over several decades.

Drug abuse patients usually seek clinical help in response to some coercive force, either external (e.g., family, work supervisor) or internal (e.g., malaise, depression). An important step in management involves delineating this coercive force. Complicating this process is the patient's frequent lack of awareness regarding the relationship between the current problem and the drug use. Another obstacle may be a tendency to blame others for the current problem rather than to take responsibility for the problem. As with other elements of the addictive course, social consequences and malfunction tend to advance over time; see Table 15.6.

Since drug abuse may present with various surgical, medical, or psychiatric problems, the clinician will want to inquire routinely about each patient's use of drugs. See Table 15.7 for the biomedical harbingers that mark the addicted person's deteriorating health. In order to rule drug abuse in or out, the physician must know each patient's drug use type, dose, duration, pattern of use, and route of administration. Drug abuse patients typically do not volunteer symptoms indicative of depression, anxiety, panic, or psychosis. Specific inquiry is necessary.

TABLE 15.4. Phases of: psychological factors in substance use disorder.

Characteristic	Early phase: problematic usage	Middle phase: chronic dependence, addiction	Late phase: deterioration
Motivation	Uses to enjoy, build up confidence, relieve insomnia and anxiety, etc.; use becomes increasingly important	Uses to feel normal; use is as important as family, friends, work	Enjoys usage less but cannot stop; use becomes the central element of person's life
Emotional concomitants	Mood swings related to usage (anger, remorse, anxiety, shamed or anxious regarding usage); feels weak and remorseful	Personality change and increasing emotional lability; ambivalent about usage; feels guilty, resentful, inadequate, and inferior	Erratic, suspicious, and often apathetic; defensive regarding usage; feels alone, deserted
Cognitive processes	Obsesses regarding next usage; reduced interests and ambition; focuses thoughts and conversation on chemical usage	Increasing self-pity, deteriorating self-image; self-deception regarding usage and effects; loses sense of time	Confused, projects own problems onto others; unable to conceptualize current status objectively
Judgment, insight	Begins to exercise poor judgment; still able to extricate self from most problems; episodic insight and concern with drug or alcohol usage	Large proportion of decisions lead to problems; problem solving increasingly ineffective; avoids being insightful, although capable of insight	Extremely poor judgment in most matters; unable to solve own problems; is not insightful even during abstinent intervals

TABLE 15.5. Phases of behavioral factors in substance use disorder.

Characteristic	Early phase: problematic usage	Middle phase: chronic dependence, addiction	Late phase: deterioration
Drug usage	Increasing amounts and frequency of use	"Titer" or "binge" usage; attempts at abstinence	Continuous usage; uses "substitute" intoxicants
Control over usage	Begins attempts to decrease amounts or frequency of use	Begins to lose control (takes more than intended or for a longer period than intended)	Loses control most of the time
Drug-related behavior	Seeks occasions to use; chooses friends who use heavily; may begin to be secretive about usage	Increased need to use at specific times and places; develops ingenuity at obtaining, paying for, hiding, and using drug	Compulsive usage, despite many problems associated with usage and decreased enjoyment from drug or alcohol; plans daily activities around usage
Drug effects on behavior	Episodic intoxication, dysarthria, and emotional lability; attempts to hide drug or alcohol effects from others	Impairment between intoxication episodes: trite expressions and "non sequiturs" prevail in conversation; fatigue; decreased productivity	Poor grooming and disheveled dress; lack of interest in appearance; unconcern with opinions of others

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TABLE 15.6. Phases of social factors in substance use disorder.

Characteristic	Early phase: problematic usage	Middle phase: chronic dependence, addiction	Late phase: deterioration
Interpersonal relationships	Changes associates, from abstainers to moderate users to heavy users	Alienates others by arguing, embarrassing, and taking advantage; breaks promises and lies	Manipulates others to obtain drug or alcohol; compensatory bragging
Family	Argues with family over usage; spends less time at home; neglects family emotionally	Abuses family by lying, stealing, or fighting; spends most of time away from home	Alienated from family; lives away from family
Employment	"Monday morning" absenteeism; conflict with boss	Decreased job efficiency; changes jobs often or is fired; decreasing job prestige; holds jobs for shorter periods	Day labor; unemployed, on relief or social welfare
Residence	Stable residence; lives with others	Begins moving from place to place; loses roommates and family members	Lower socioeconomic neighborhood; lives alone
School[a]	Decreasing grades; complaints from teachers	Suspension from school; school dropout	Requires special educational and rehabilitation facilities
Legal effects	May have legal problems; driving while intoxicated; disorderly; assault	Usually has legal problems and large attorney fees; may be litigious	Defaults on contractual obligations; may be imprisoned for property offenses and manslaughter
Finances	Spends family funds on drug or alcohol; may take extra job to support habit; may become extravagant	Spends ¼ to ½ of annual income on drug or alcohol; heavily in debt and bankruptcy	Spends most of income on drugs or alcohol; destitute
Social Affiliations	Discontinues social activities not involving usage (e.g., church, hobby, theater, sports)	Drops formal group affiliations (e.g., union, guild, club); begins short-lived companionship with chemically dependent persons	Becomes an involuntary client of social institutions

[a]For chemically dependent persons attending school.
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TABLE 15.7. Phases of biomedical factors in substance use disorder.

Characteristic	Early phase: problematic usage	Middle phase: chronic dependence, addiction	Late phase: deterioration
Pharmacology	Tolerance increases; larger doses used to relax and relieve insomnia or other symptoms	Withdrawal effects; blackout (for alcohol); morning or daytime usage to alleviate withdrawal	Decreased tolerance (early onset of intoxication or blackout); delirium tremens or withdrawal seizure (with alcohol or sedatives)
Common health problems	Injuries: vehicular or industrial accidents, falls, and burns	Infections: respiratory, urogenital, and skin; injuries; accidental overdosage; suicide attempts	Parenteral users: septicemia, pulmonary edema, endocarditis; alcohols: cirrhosis, pancreatitis, myocarditis; violence: injuries, homicide, suicide; nutritional problems: vitamin, protein, mineral deficiency
Sexual effects	May initially enhance sexual function	Sexual problems: impotence, frigidity, promiscuity or extramarital liaisons, and venereal disease	Difficulty obtaining sexual partner; purchase of sexual services; loss of interest in sex; prostitution to obtain funds for drug
Common symptoms	Insomnia, boredom, chronic anxiety, headache, palpitation, tachycardia, flatulence, belching, cramps, epigastric distress, irritability, puffy face or extremities	Sweating, apprehension, decreased libido, visual disturbances, myalgia, malaise, obesity, diarrhea, weight change (loss or gain), memory lapses, weak, fatigues easily, "dry heaves," depression, panic, fears	Bad taste, impotence, halitosis, cachexia, persistent abdominal pain, seizures

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Formal mental status examination may reveal unsuspected deficits in orientation, memory, or cognition. Physical examination can demonstrate evidence of parenteral injection (e.g., venous tracks, skin-popping scars), chronic smoking (e.g., rales and rhonchi), malnutrition, infectious diseases, and traumatic sequelae. Neurologic findings (e.g., ataxia, dysarthria, pupillary changes), autonomic signs (e.g., flushing, perspiration, piloerection), and vital sign abnormalities (e.g., tachycardia, hypertension) provide valuable clues. Table 15.2 lists the signs associated with various drugs.

15.5.2.1. Case Report

A 24-year-old single woman presented with opioid dependence and amenorrhea for four months. She had been discharged from military duty, following a 1-year deployment in Iraq. While in Iraq, she developed headache, insomnia, chronic anxiety, and episodic panic attacks associated with combat-related events (e.g., mortar attacks, injury and death of other service members). During a trip to a nearby country, a friend shared her prescribed opioid medication with her. Her anxiety symptoms abated, her headaches ceased, and she was able to sleep. Back in Iraq, a military provider prescribed opioids for her during the remainder of her deployment. Upon returning to the United States and civilian life, she continued taking opioids, both prescribed and not prescribed. She also "partied" with other veterans from Iraq, leading to her unplanned pregnancy. All of her nuclear family members had a substance disorder, although three were in stable recovery and one was actively abusing "street" opioids. Subsequently, she did well on maintenance opioid medication, delivering a healthy child and complying with treatment. Treatment of her chronic anxiety, secondary mood symptoms, solo parenting, and maturation from a "child of addicts" background posed many challenges in her intermediate term care.

This case exemplified the prominence of iatrogenic (as opposed to "street") opioids in current practice. Exposure to opioids via a friend's opioid prescription, preexisting anxiety symptoms, familial–genetic factors, and casual opioid prescribing all facilitated her addiction. Sudden separation from the military, a post-deployment "party" subculture with casual sexuality, and familial predisposition also fostered her vulnerability to opioid dependence. Maintenance opioid therapy contributed to a healthy newborn and abstinence from drug seeking but was not sufficient to alleviate the psychosocial obstacles that she faced. Her struggle continued over several years, with alternating relapse and recovery efforts.

15.5.3. Analysis of the Findings

Acute drug-related problems are generally related to pharmacologic actions of the drug itself or the route of administration. These include intoxication, overdose, and medical emergencies such as agitated delirium or trauma—or, as in this case, intrauterine pregnancy. The initial problems were due to psychosocial challenges from flawed child raising, combat exposure, lax prescribing practices, and a post-deployment "party" subculture. Special clinical presentations depended on the patient's age, gender, family history, drug exposure, and the setting.

15.6. Clinical Course

The typical course of untreated, chronic drug abuse is deterioration over a period of years, often with periods of relative stabilization or brief improvement followed by further deterioration. Acute problems associated with recent drug abuse may cause the disorder to be self-limiting if the consequences motivate the user to moderate or cease drug usage. However, spontaneous abstinence from drugs occurs infrequently among those with recurrent episodes of drug abuse or with chronic drug dependence. Disability or premature death may ensue in time.

Progression over time likewise varies with the drug, route of administration, various host, and environmental factors. Other things being equal, routes with rapid drug onset (i.e., injection, smoking, snuffing) hasten the morbid course over slower routes of administration (e.g., ingestion, chewing). Drugs with shorter half-lives (e.g., heroin, lorazepam, cocaine) lead to a more rapid course than those with longer half-lives (e.g., opium, diazepam, amphetamine). More potent drugs (e.g., morphine) hasten and increase the morbid effects over weaker drugs in the same category (e.g., codeine). Some drugs produce typical medical complications (e.g., tobacco) or neuropsychiatric complications (e.g., phencyclidine) as their first manifestation, while others are more apt initially to produce psychosocial consequences (e.g., sedatives, opioids). Drugs with potent effects, rapid onset, and shorter half-lives (e.g., cocaine, heroin) lead to treatment within about 3 years of initiating their drug abuse, whereas drugs with less potent effects, slower onset, or longer half-lives (e.g., diazepam, opium) may continue 10 years or longer before treatment results (48).

Age at onset influences the course, so opioid dependence beginning at age 15 affects the patient's life course differently from opioid dependence beginning at age 35 or 55 years. Younger individuals have not yet had the opportunity to complete their education, learn an occupation, become employed, marry, have children, or otherwise establish some social competency. Normal phases of psychosocial maturation lag or fail to evolve in the face of severe drug abuse. Older drug abusers

TABLE 15.8. Phases of treatment approaches in substance use disorder.

Characteristic	Early phase: problematic usage	Middle phase: chronic dependence, addiction	Late phase: deterioration
Prognosis without treatment	Some spontaneously improve, some progress to later stages	Small percentage (<10%) spontaneously improve; most progress to later stage	Virtually no spontaneous improvement; a few "plateau"; most deteriorate rapidly
Most effective treatment modalities	Mutual-help groups; marital and family therapy; pharmacotherapy for 1–2 years (e.g., antidepressants, disulfiram, anti-craving, medication); partial hospitalization (e.g., day only, evening only, weekend only)	Pharmacotherapy (e.g., buprenorphine, methadone, disulfiram, anti-craving, medication); mutual-help groups; marital and family therapy; intensive outpatient program, long-term outpatient treatment program, and halfway house	Pharmacotherapy (e.g., buprenorphine, methadone, disulfiram, anti-craving, medication)/intensive outpatient program; residential treatment: special long-term units, nursing home, quarter-way house, mutual-help groups
Prognosis with treatment	Optimal: 60–80% "significantly improved" at 1 year post-treatment	Good: 40–60% "significantly improved" at 1 year posttreatment	Fair: 10–40% improved at 1 year; high mortality and morbidity rate in remainder
Cooperation with treatment	Willing to undertake a prolonged period of abstinence, see physician regularly, and follow treatment recommendations	May enter treatment only with pressure by family, employer, court, friends, and physician	May need to be coerced by society (e.g., incarceration, legal commitment into treatment)

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coming to treatment usually have more biomedical problems and social isolation; younger drug abusers experience more legal, occupational, and family problems.

Tables 15.4, 15.5, 15.6, 15.7, and 15.8 describe phases in the course of drug abuse. Course progression is not always as consistent as shown in the tables. A patient may show early changes in some areas and more advanced changes in other areas.

Treatment often, but not always, alters the natural course of drug abuse. See Table 15.8 for prognosis with and without treatment, fitting treatment to addiction phase, and typical levels of treatment compliance across phases. In general, treatment earlier in the course tends to be more effective and less costly. Later treatment, especially after occupational loss and alienation from family, is less apt to be effective. Even in advanced cases, however, treatment often reduces the patient's morbidity and may set the stage for eventual recovery. Assuming that patients cannot recover, and that chronic deterioration is inevitable, can set up a self-fulfilling prophecy.

Acute phases of recovery, precipitated by medical, psychiatric, or social crises, proceeds over several weeks. Treatment involves medical stabilization, crisis intervention, and an assessment of psychosocial resources and liabilities. The intermediate phase of recovery involves autonomic nervous system stabilization (e.g., stable vital signs, normal gastrointestinal function), resolution of emotional distress, and social reentry; it continues over several months. In successful recovery, psychological well-being, social fulfillment, and occupational stability in the final phase of recovery typically require several years.

Brief but increasingly less frequent return to drug abuse often occurs during the early months of recovery. Although pharmacologic factors greatly influence the pretreatment course, the posttreatment relapse rates for heroin, alcohol, and tobacco (in the absence of ongoing outpatient treatment) are remarkably similar, as shown in Fig. 15.1. Modern treatment methods have changed the shape of this curve appreciably by increasing the 1-year recovery rates—often as high as 35–75 % depending on the substance, the treatment, and the characteristics of the patient group.

15.7. Laboratory Findings

Laboratory tests for drug abuse are of two general kinds. One set of tests involves direct assessment of drugs, such as drug levels in body fluids. Another set of tests involves indirect biochemical, physiologic, and psychological tests to assess the extent of impairment produced by drugs, such as hypovitaminosis, secondary infections, or psychosocial dysfunction (e.g., unemployment). These tests augment but cannot substitute for a thorough history, psychiatric interview, mental status assessment, and physical examination. Collateral sources of information may include medical or other records, reports from family or friends, as well as information from other professional sources (e.g., teacher, court, probation officer). Another assessment technique is the "test of time," in which the individual is observed and reassessed over time in order to assess the severity of the condition and the potential for recovery.

Many drugs of abuse or their metabolites can be found in urine for 12–48 hours after the last dose and sometimes longer in the case of chronic use (e.g., cannabis, amphetamine, benzoylecgonine). Qualitative urine tests are useful for screening in high-risk situations, such as emergency rooms, orthopedic and psychiatric hospital admissions, and certain target groups

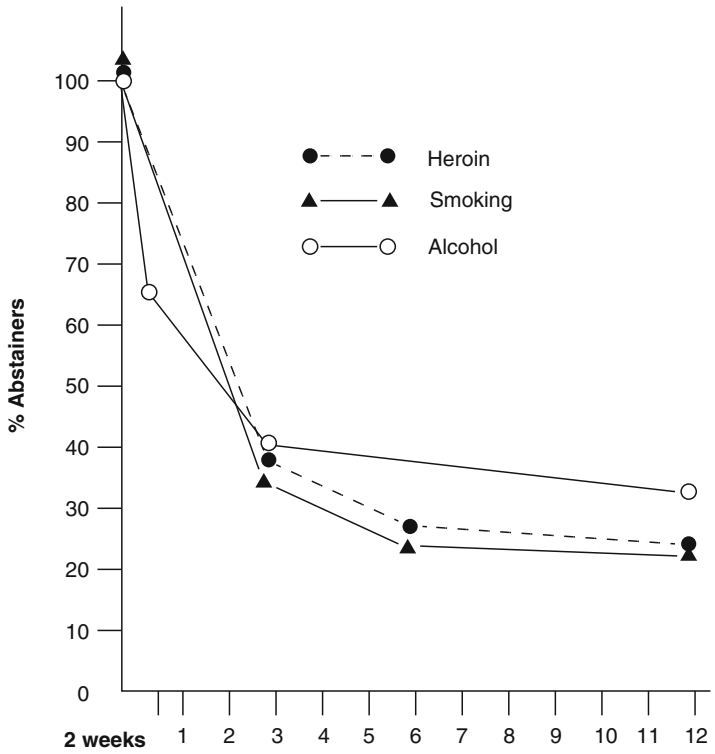

FIGURE 15.1. Relapse rate over time for heroin, smoking, and alcohol. From: Figure 15.1 reprinted from relapse rates in addiction programs, Hunt WA, Barnett LW, Branch LG, Journal Clinical Psychology 27:455–456, Copyright (1971) John Wiley and Sons.

(e.g., trauma victims, brittle diabetics, treatment failures). Quantitative blood measures are usually required only for special instances, such as management of overdose or forensic evaluation. Naloxone challenge, specific for the diagnosis of opioid dependence, consists of administering parenteral naloxone and observing for the opioid withdrawal syndrome.

Other laboratory tests not specifically measuring drugs can aid in assessing the severity of the drug abuse problem. Acute intoxication or recent withdrawal may produce abnormalities on the electroencephalogram, which can suggest specific drug effects to the experienced electroencephalographer.

Biochemical tests for renal and hepatic function reflect drug-related tissue damage to these organs. Vitamin (e.g., carotene or folic acid), serum iron, and serum protein levels can reveal nutritional neglect. With chronic drug abuse, many patients experience mild-to-moderate endocrine dysfunctions reflected in abnormal thyroid tests, electrolyte disturbances, hyperglycemia or hypoglycemia, and/or an abnormal dexamethasone suppression test. Chronic smoking can produce increased respiratory dead space, decreased vital capacity, prolonged rate of timed expiration, and abnormal blood gases. Parenteral injection of drugs can give rise to chronic viremia (hepatitis B and C, HIV), positive blood cultures, an elevated sedimentation rate, high white blood cell count, or an increased gamma globulin fraction in the serum protein. Depending on the psychiatric picture, abnormalities may occur on personality tests (e.g., the Minnesota Multiphasic Personality Inventory), intelligence tests (e.g., Wechsler Intelligence Scales), and organicity tests (e.g., Bender-Gestalt). Traumatic injuries (from fights or falls) may show up on x-rays as healing fractures of the ribs or extremities or on neuroimages as damaged or poorly perfused brain tissue. Electrophysiological measures may reveal abnormal, possibly pathognomonic abnormalities (49).

Response to treatment can be assessed by following both the first category of tests (e.g., direct drug measures) and the second category (e.g., tests of impairment or secondary complications), especially when these have been abnormal previously.

15.8. Differential Diagnosis

Differentiating drug abuse from other psychiatric disorders can be difficult. Substance abuse and psychiatric disorder coexist in one-quarter to one-third of psychiatric inpatients and in about the same or higher proportion of substance abuse patients. Drug abuse may develop as an attempt at self-treatment for a preexisting disorder (e.g., stimulant abuse for depression, sedative abuse

for anxiety or mania). Or secondary psychiatric disturbances (e.g., depression, panic attacks) may appear during the course of drug abuse or during recovery from drug abuse. Secondary sociopathy may attend the disinhibiting effects of certain drugs. Hostile-dependent behavior is a common secondary behavioral manifestation that usually clears with successful recovery.

Drug effects may mimic psychiatric disorders. For example, caffeine, cocaine, or amphetamine intoxication can produce symptoms like those of anxiety or mania. Withdrawal from these drugs may resemble depression or, less often, paranoia. Acute cannabis, phencyclidine, or hallucinogen intoxication may present clinically as acute psychosis, manic psychosis, or delirium due to a medical condition.

Drugs also may precipitate psychiatric syndromes, which persist well beyond the drug effect in the body—a phenomenon called "kindling." Acute or chronic use of cocaine, amphetamine, cannabis, phencyclidine, and the hallucinogens may bring about a lengthy illness indistinguishable from schizophrenia or bipolar illness. In some cases, the drug-precipitated disorder (once successfully treated) does not recur. In other cases, the disorder may recur even without subsequent drug abuse, as in this case.

15.8.1. Case Report

A 19-year-old college student became acutely and floridly psychotic following her first use of hashish. She failed to respond to high doses of antipsychotic medication prescribed over several weeks but did recover with a course of ECT and subsequent antipsychotic treatment. A discharge diagnosis of schizoaffective disorder was made. Over the subsequent year, her medication was reduced without incident. She later completed graduate school, worked for a few years, and married. Within weeks following the birth of her third child, at age 31, she developed insomnia, racing thoughts, euphoric mood, grandiose plans, and poor judgment (but without hallucinations or delusions). Antipsychotic medication (in low doses) along with lithium, prescribed on an outpatient basis, led to resolution of her symptoms over several weeks.

In this case it appears that drug abuse may have precipitated as well as exacerbated the first episode. The second episode, without drug abuse, was milder and responded more readily to treatment. The patient's course suggests that hashish alone did not produce the first illness but rather precipitated the illness in a person with a premorbid potential for mood disorder.

Drug effect from opioids, sedatives, stimulants, cannabis, phencyclidine, and the hallucinogens, as well as the volatile hydrocarbons, may produce an acute brain syndrome due to substances, with confusion and delirium. Chronic brain syndrome due to substances is less common but can occur. Certain volatile hydrocarbons can, with chronic use, produce dementia pictures similar to alcohol-induced dementia. Sedative and opioid abusers also may demonstrate it, probably from recurrent hypoxia secondary to respiratory depression or from head trauma due to falls or fights. Caffeine and tobacco may produce chronic brain syndromes indirectly as a result of secondary medical complications (e.g., hypertension, emphysema).

15.9. Treatment

15.9.1. Drug-Related Emergencies

Intoxication is managed simply by observing and protecting the individual until the drug is metabolized or excreted. It is important to ensure that the patient does not injure self or others while the drug is being metabolized and/or excreted. Involuntary hospitalization may be necessary for 2 or 3 days during this phase.

Overdose is managed on medical or psychiatric units, depending on the nature of the problem and the type of drug. Specific antidotes are available for three drug types liable to abuse: opioids, anticholinergics, and benzodiazepines. Naloxone for opioid overdose and physostigmine for anticholinergic overdose share two common features. First, dosage must be individualized for each patient, and second, repeated doses at 2- to 3-hour intervals are necessary because their duration of action is considerably shorter than those of many drugs of abuse (particularly when taken in large doses). Flumazenil can be used as the benzodiazepine antagonist, but it is seldom used due to potentially serious complications. Rarely, dialysis may be necessary for sedative overdose; very high blood levels, rapidly progressing stupor, and depression of vital signs comprise indications for dialysis. Acidifying the urine hastens the excretion of phencyclidine and amphetamines, while alkalinization aids excretion of some barbiturates.

Withdrawal treatment hastens recovery, reduces mortality, and aids in establishing the doctor–patient relationship. It may induce the suffering patient, still ambivalent about giving up drug dependence, to enter treatment. Opioid and sedative withdrawals are managed by using a long-acting drug that is cross-tolerant with the drug being abused. Some clinicians use antidepressant or stimulant drugs for more severe cases of stimulant withdrawal, but minimal pharmacotherapy is needed in most stimulant withdrawal. The first step consists of administering enough drug to make the patient comfortable, even to the point of mild sedation. Patients in severe withdrawal may require the first dose intravenously, since the toxic patient may not absorb well via oral ingestion or subcutaneous injection. The half-life of the drug administered should be at least as long as that

of the drug being abused and preferably longer (e.g., diazepam for lorazepam dependence, methadone for heroin dependence). Otherwise, the patient will be in and out of withdrawal, frequent doses will be necessary, and the withdrawal will be stormy and prolonged. For sedative withdrawal, some clinicians prefer to administer a shorter-acting drug initially in case the patient requires respiratory assistance with the stabilizing dose. Duration of the withdrawal is shorter for short-acting drugs and longer for longer-acting drugs. For short-acting drugs, such as lorazepam or heroin, 3- to 5-day withdrawal regimens are adequate for resolution of acute symptoms. Intermediate-acting drugs, such as clonazepam or opium, require 10–20 days depending on the degree of dependence and the patient's medical condition. Longer withdrawal regimens, lasting up to several weeks or a few months, may be needed for the long-acting drugs that accumulate in the tissues and are slowly released, such as diazepam and ethchlorvynol. Doses should be administered on a routine basis rather than as requested by the patient. For example, a 20% daily reduction would cover a 5-day withdrawal or 10% daily reduction for a 10-day withdrawal. Some mild insomnia or discomfort may still occur during withdrawal treatment. Symptom-relieving drugs (i.e., analgesics, sedatives, antiemetics) may alleviate the latter but may mask underlying medical or psychiatric disorders (48).

Methadone, a μ-opioid receptor agonist, differs from most other drugs in that the half-life (the duration of half of the absorbed dose in the body) increases with larger doses over time (50). At 5 mg administered four times a day, the half-life resembles that of morphine (3–4 hours). Repeated daily doses above 20 mg per day gradually increase the half-life to 12 hours and beyond. Non-tolerant individuals may experience respiratory depression at doses in the 30–40 mg range. Clinicians using methadone for opioid withdrawal treatment should be experienced, as fatal iatrogenic overdoses have resulted in the hands of clinicians unfamiliar with opioid withdrawal manifestations or methadone pharmacokinetics. Alpha2-adrenergic agonists (e.g., clonidine, lofexidine) are other options to alleviate opioid withdrawal by controlling autonomic symptoms. Common medical complications associated with drug abuse should be considered early during patient assessment. These include nutritional abnormalities, acute and chronic infections, and occult trauma (e.g., subdural hematoma).

Buprenorphine withdrawal also presents some unusual characteristics (36). Case reports show that withdrawal is mild and lasts only a day or two, regardless of dosage (51). This phenomenon may be due to the strong affinity and slow release of buprenorphine from the mu receptor site. Small withdrawal doses may simply prolong withdrawal.

Referral to special drug treatment programs may be necessary if those providing early medical care do not have resources and skills for further treatment. Patients commonly view such a referral as a rejection by the physician. This can be avoided by making an appointment for the patient a few weeks after the referral. The follow-up appointment assures the patient that the clinician is not abandoning him or her and provides an opportunity to assess the efficacy of the referral.

15.9.2. Assessing the Phase of Recovery

The following phases of treatment entry and recovery have been validated (52):

- Precontemplation: drug user has given no thought to stopping drug use or seeking help.
- Contemplation: drug user has considered cutting back or stopping drugs or seeking help.
- Preparation/determination: drug user has decided to cut back or stop drugs or seek help.
- Action: drug user has cut back or stopped use or sought help.
- Maintenance: former drug user maintains sobriety through pro-sobriety affiliations and activities to prevent relapse.

Discovering the drug user's preparedness for recovery is key to successful intervention. Assisting the patient through this process may require many months, although it can happen rapidly in crises.

The critical element lies in the clinician's undertaking interventions that are matched to the drug user's recovery phase. Pushing an action when the patient is in the contemplation stage will not work. At that stage, the goal is to assist the patient in moving from precontemplation to contemplation.

15.9.2.1. Case Report

The police brought a 19-year-old man to the emergency room with facial lacerations sustained in a fight at a music concert. He had consumed two pills given to him by friends, which he assumed were "herbal highs." A regular drug and alcohol user since age 15, he had recently moderated his use following the suicide death of his best friend several weeks earlier. He initially refused referral to care, as he thought his drug use was not out of control. The ER resident obtained a urine toxicology screen, called the patient's mother to pick him up, and contacted the psychiatry resident. The urine screen revealed methadone and a benzodiazepine, to the patient's surprise. In a dialogue with the patient and his mother, the psychiatry resident established that the mother had become alarmed at the patient's deterioration and considered court commitment. At the end of several hours in the ER, the patient concurred that his drug use had escalated beyond his control, and he agreed to an outpatient consultation the next day in the company of his mother.

In this case, the patient moved from precontemplation to contemplation ("I need to cut back") and then to a decision ("I will go to an evaluation with my mother"). He followed this through with an action (showing up for the evaluation). The unusual rapidity in this case was probably due to several concurrent crises: the recent death of his friend, his consuming drugs whose contents he did not know, an avoidable and disfiguring injury to his face, the unexpected urinalysis results, discovery of his mother's plans, and the resident's conveying to the patient that he had a drug abuse diagnosis (heavy pattern of use, continued use despite a series of drug-related consequences).

15.9.3. Treatment Modalities

Modalities for treatment of drug abuse are numerous and include the following: Psychotherapies and sociotherapies include individual, couple, family, and group therapies; relapse prevention therapy; motivational enhancement and verbal aversion therapies; contingency contracting therapy; social skills learning; and day, evening, or weekend program; these approaches assume sobriety, a stable residence, and some daily employment or other productive activity.

Pharmacotherapies: Several old and new medications have been used to manage addictions, not only for detoxifications but also for relapse prevention. For the treatment of severe opioid dependence, methadone and buprenorphine maintenance programs have been successful in decreasing illicit opioid consumption as well as medical, social, and legal consequences related to opioid use. Buprenorphine, a partial μ-opioid agonist and a κ-opioid antagonist approved by the FDA for treating opioid dependence can be prescribed in a primary care office setting instead of highly regulated methadone programs. Buprenorphine has less abuse potential and better safety profile than methadone. During the induction phase, buprenorphine is initiated while monitoring the patient daily for 3–7 days until a stable dose is reached. Typically, the induction doses are 2–8 mg daily, with 4–8 mg daily increases. During the maintenance phase, most patients take between 8 and 24 mg of sublingual buprenorphine. Buprenorphine can be also used as a transition medication from illicit opioid drugs to naltrexone. Naltrexone is a μ-opioid antagonist and blocks the euphoric effects of opioids. Supervision, monitoring, and contingency management are required to increase compliance with naltrexone. Monthly naltrexone injection can prevent relapse for patients recovering from opioid use disorder.

Several medications have been approved by the FDA for alcohol dependence: disulfiram, naltrexone, acamprosate, and long-acting injectable naltrexone.

No medication has been approved by the FDA for the treatment of cocaine dependence, but several medications have been reported effective in clinical trials. These agents work by increasing dopamine levels (disulfiram, amantadine, bromocriptine), enhancing GABA system (baclofen, carbamazepine, tiagabine), or decreasing adrenergic activities (propranolol) (53).

For tobacco dependence, several medications have been approved by the FDA and widely used in primary settings. These interventions include nicotine replacement therapy (transdermal nicotine patch, gum, nasal spray, nicotine inhaler, lozenge) or non-nicotine oral agents (bupropion, varenicline). Nicotine and cocaine vaccines have been under investigation.

Somatotherapies: electroacupuncture (54) has proven beneficial for opioid withdrawal and for maintenance of selected cases.

Residential treatment includes special recovery-oriented residential facilities, halfway houses, and therapeutic communities; these alternatives can be useful for the unemployed or homeless patient.

Properly speaking, mutual-help groups are not a form of treatment, although often quite therapeutic. They include Narcotics Anonymous, Alcoholics Anonymous, Al-Anon (for relatives or friends of those with substance use disorders), and other drug-specific, ethnic-specific, gender-specific, or occupation-specific groups. These groups can be useful at any phase of recovery, from precontemplation to maintenance.

If major psychiatric problems persist beyond a few to several days in association with substance use disorder, these problems will probably not resolve spontaneously. Continuation of major depression, psychosis, mania, and other major disorders beyond 2 weeks almost always calls for specific treatment and rehabilitation rather than expectant observation. If the patient responds rapidly and completely to low doses of medication, a lengthy course of medication may not be needed. Close monitoring should accompany a slow medication taper in such cases.

Minor or less disabling psychiatric syndromes are common in the early weeks of recovery. These may include adjustment reactions, a period of generalized anxiety, or a few panic attacks. If these are decreasing in severity and becoming less frequent, specific treatment may not be necessary. On the other hand, increasing, severe, or disabling symptoms generally require psychiatric treatment.

15.9.4. Treatment Goals, Outcome, and Efficacy

Treatment for drug abuse may be aimed at total abstinence, reduction of drug use, or removal of problematic aspects of continued drug use. Generally, abstinence, temporary or permanent, is the explicit goal. Simple reduction in drug dose, with continued use, is rarely effective over the long term but may result in a temporary reduction in symptoms or problems. Licit substitution of illicit opioid consumption in methadone or buprenorphine maintenance programs can appreciably help selected patients.

Treatment success is related to many factors besides treatment modalities themselves. As indicated above, matching treatment approach to the patient's recovery phase is critical. In addition, patients who are doing better at the end of 1- and 2-year follow-up studies show one or more of the following characteristics vis-à-vis treatment:

- Occupied as employees or students.
- Residence with the family or with sober persons.
- Treatment-seeking earlier rather than later in the event of relapse.
- Compliance with treatment recommendations.
- Involvement of the family in treatment.
- Continued treatment or self-help on a regular basis over 1 or more years.
- Pharmacotherapy, as warranted and appropriate to the case, by controlling drug cravings and stabilizing the central nervous system related to drug addictions.
- Treatment of comorbid psychiatric disorders: Psychiatric symptoms are much more frequent in patients with addictive disorders. Anxious and depressed addicts tend to relapse readily after addiction treatment. Proper evaluation and treatment of comorbid psychiatric disorders can contribute to relapse prevention.

Acute detoxification and medical management alone tend to have limited long-term efficacy. This is also true of residential treatment alone without subsequent outpatient care. Under such circumstances, the rate of abstinence 1 year following discharge is low. With continued outpatient care, plus case management in severe cases, the rate of abstinence at 1 year can range higher. Since those abstinent and doing well at the end of 1 year have good outcomes in most cases, the first year of outpatient care is critical.

Cost/benefit from treatment also must be considered. For decades treatment research did not take into account cost, skills of clinic staff, and applicability of treatment approaches to patients in community settings (55). In recent years a national Clinical Trials Network (CTN) has tested not only treatment efficacy but also the feasibility of drug addiction treatment in community settings (56). This CTN initiative, combined with increased understanding of addiction neurobiology (57), is forging links between professional resources and community-based, patient-centered, recovery resources (such as mutual-help groups, "drug courts," and monitored residential facilities).

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16
Sexual Disorders: Dysfunction, Gender Identity and Paraphilias

Jon E. Grant, M.D., J.D., M.P.H. and Nancy C. Raymond, M.D.

Abstract Sexual disorders in the Diagnostic and Statistical Manual for DSM-5 are divided into three major categories: 1) sexual dysfunctions, problems in sexual desire or disturbances in the psychophysiologic changes that are part of the sexual response cycle, 2) Paraphilias, which involve recurrent intense sexual urges or fantasies, or behaviors that involve unusual objects, activities, or situations that are by and large not culturally sanctioned, and 3) gender identity disorders, which are characterized by dissatisfaction with one's biological gender and often a desire to undergo gender reassignment. In this chapter we will review the diagnostic criteria, prevalence, etiology, assessment and treatment of these disorders.

Keywords Sexual dysfunction • Paraphilias • Gender identity disorder • Sexual health • Compulsive sexual behavior

16.1. Introduction

Sexual disorders in the Diagnostic and Statistical Manual for DSM-5 (1) are divided into three major categories:

1. Sexual dysfunctions. Problems in sexual desire or disturbances in the psychophysiologic changes that are part of the sexual response cycle.
2. Paraphilias, which involve recurrent intense sexual urges or fantasies, or behaviors that involve unusual objects, activities, or situations that are by and large not culturally sanctioned.
3. Gender identity disorders, which are characterized by dissatisfaction with one's biological gender and often a desire to undergo gender reassignment.

Psychiatric research in the sexual and gender identity disorders lags behind research in many other areas of psychiatry. Less is known about the associated disorders, course, familial patterns, and etiology. Prior to summarizing the criteria, prevalence, assessment and treatment of the sexual disorders we will present a brief discussion on the determinants of sexual health.

J.E. Grant, M.D., J.D., M.P.H. (✉)
Professor, Department of Psychiatry and Behavioral Neuroscience,
University of Chicago Pritzker School of Medicine, Chicago, IL, USA
e-mail: jongrant@uchicago.edu

N.C. Raymond, M.D.
Professor, Department of Psychiatry, University of Minnesota School of Medicine, Minneapolis, MN, USA
e-mail: raymo002@umn.edu

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16.2. Sexual Health Defined

The World Health Organization (WHO) and others have arrived at an understanding of the components of sexual health (2–5). According to these sources, sexual health is an approach to sexuality founded in accurate knowledge, personal awareness, and self-acceptance where one's behavior, values, and emotions are congruent and integrated within a person's wider personality structure. The definition of sexual health involves the ability to choose to be intimate with a partner, to communicate explicitly about sexual needs and desires, and to be sexually functional, to have desire, become aroused, and attain sexual fulfillment. It also involves acting intentionally and responsibly and having the ability to set appropriate sexual boundaries. Additionally, sexual health has a communal aspect reflecting not only self-acceptance and respect but also respect and appreciation for individual differences and diversity. Sexual health includes a sense of self-esteem, personal attractiveness and confidence, as well as freedom from sexual dysfunction, sexually transmitted diseases, and sexual assault and coercion. Sexual health affirms sexuality as a positive force enhancing other dimensions of one's life. In treating all of the sexual disorders described below the goal should be to assist the patient in achieving a healthy expression of their sexuality.

16.3. Sexual Dysfunction Disorders

Sexual Dysfunctions are disorders characterized by a disturbance in sexual functioning or desire (Table 16.1). DSM-5 provides subtypes and specifiers for each of the Sexual Dysfunctions. Whereas the subtypes are carried over from DSM-IV-TR, the specifiers have been expanded to more accurately reflect the variety of factors that can impact sexual functioning. The subtypes of *lifelong* and *acquired* refer to the onset of the sexual dysfunction. Lifelong refers to the failure to develop normal sexual functioning at puberty which then persists, whereas the acquired subtype refers to situations in which the person develops sexual dysfunction after having had normal functioning. Specifiers include *Situational* and *Generalized*. The Situational subtype refers to sexual dysfunction that occurs only in certain situations, with certain types of sexual stimulation, or with particular partners. The generalized type refers to sexual dysfunction that occurs independent of the situation, the partner or the type of stimulation. The Situational subtype is less likely to be due to a medication side effects or a medical condition. In addition, DSM-5 provides additional specifiers. Sexual dysfunction often occurs within a relationship and therefore *Partner factors* (e.g., a partner's erectile problems) may play a role as well as *Relationship factors* (e.g., sexual incompatibility). In these contexts, it may be difficult to determine whether the partner or relationship factor gave rise to the sexual dysfunction, results from the sexual dysfunction, or the two are interactive. Individual vulnerability factors, cultural/religious factors, and contributory medical factors are also explicitly listed in DSM-5 as contributing to or playing a role in the sexual dysfunction. These specifiers recognize that in many cases, the causes of sexual disorders are multifactorial and many variables may partially contribute to the etiology of a disorder.

16.3.1. Male Hypoactive Sexual Desire Disorder

According to the DSM-5, hypoactive sexual desire disorder is characterized by a recurrent lack of interest in or thoughts about sex (1). As with all of the other sexual dysfunction disorders, the disturbance must cause marked distress and the dysfunction should not be due to another psychiatric disorder or the physiologic effects of a substance or general medical condition. One of the complexities of making this diagnosis is that the clinician makes the judgment as to whether the man's

TABLE 16.1 Categorization of sexual dysfunctions.

Sexual dysfunction	Diagnostic criteria
Male hypoactive sexual desire disorder	Decreased interest in sex or thoughts of sex.
Female sexual interest/arousal disorder	Chronic problems with attaining or maintaining sexual desire.
Erectile disorder	Problems sustaining an erection.
Female orgasmic disorder	Chronic inability to achieve orgasm.
Delayed ejaculation	Chronic delay in achieving orgasm.
Early ejaculation	Problem of achieving an orgasm too quickly.
Genito-Pelvic pain/penetration disorder	Chronic pain associated with intercourse.

interest in sex is deficient (1). This of course assumes that the clinician has received adequate training on sexual functioning in men and women across the life cycle. If this has not been covered in the individual physician's training it places the burden on the practitioner to make sure they have educated themselves on this topic. The DSM-5 also emphasizes the importance of assessing the patient and partner for desire discrepancy since an apparent low desire in one partner may actually reflect the unusually high desire in the other partner.

DSM-5 has made significant changes in Hypoactive Sexual Desire Disorder. The current disorder only applies to men who have diminished desire for sexual activity and few if any sexual thoughts or fantasies. DSM-5 has created a new diagnosis for low sexual desire and arousal problems in women (i.e., Female Sexual Interest/Arousal Disorder). Other than the general changes to the category of Sexual Dysfunction in DSM-5, as stated above, the criteria for Male Hypoactive Sexual Desire Disorder are essentially unchanged from DSM-IV-TR.

16.3.1.1. Prevalence

Most studies that have reported on rates of hypoactive sexual desire disorder (HSDD) have used the DSM-IV-TR criteria and have found that in individuals between the ages of 18 and 59, 15.8% of men report persistent low desire (6). The prevalence of HSDD increases with aging particularly above the age of 60 (7).

16.3.1.2. Etiology

Low desire can be due to psychological factors, medical factors or some combination of factors. Often it is difficult to distinguish the etiology of the disorder. Biological factors include general medical conditions, psychiatric disorders, or disorders of the genitals in men. A multitude of medications and legal or illegal substances can also diminish sexual desire, including medications prescribed by psychiatrists: for example, serotonergic reuptake inhibitors, tricyclics, and monoamine oxidase inhibitors, antipsychotic medications, sedative hypnotics, and stimulants can all lower sexual desire (8). Other categories of medications that are particularly problematic are anti-hypertensives, including the beta-blockers and calcium channel blockers, intramuscular depo provera used for birth control, and any medications that bind testosterone (9, 10).

There are many psychosocial factors that affect desire, including discord in the relationship, psychosocial and life stressors, major life changes, such as marriage, divorce, change in job, health problems in family or children, or occupational stress (11). Finally, presence of other sexual disorders can affect desire. Clearly, any of the sexual pain disorders are likely to be associated with low desire. Discomfort with sexual orientation or gender identity disorder can all affect desire. Low desire disorders are not necessarily associated with orgasmic disorders and patients suffering from desire disorders still may be able to experience orgasm with adequate stimulation.

16.3.1.3. Assessment

Assessment of patients with low desire must include a thorough psychiatric and psychosocial history. Patients with low sexual desire should receive a general medical evaluation that includes screening for disorders such as cardiovascular disease, diabetes, or neurologic conditions that can affect sexual desire. A genital examination should be done to rule out infection, poor or excessive hygiene, or other medical abnormalities as causes of the low desire. Laboratory studies should include thyroid function tests, as either hypo- or hyperthyroidism can be associated with changes in sexual desire, hemoglobin, and testosterone levels, and any other labs as indicated by the history or physical exam (11). Low testosterone in men may be a factor that contributes to low sexual desire (12) so obtaining a level can be useful.

16.3.1.4. Treatment

While it is crucial to do a medical and sexual function work up on patients with low sexual desire, the majority of the time there are no clear biological findings. Frequently, treating or correcting the biological problem or even reducing or changing medications when indicated does not reverse the low desire. Psychotherapy by a therapist trained in treating sexual disorders is generally indicated.

Treatment of low sexual desire involves first identifying and treating any underlying medical conditions, replacing medications that may be affecting low desire, if possible, or substituting them for medications that have less effect on desire. Psychosocial issues must be addressed. For instance, presence of emotional or sexual abuse and general health issues must

be addressed. Issues of fatigue, depression and anxiety, lack of leisure time, sexual desire discrepancies, and communication difficulties are often contributing factors that need to be examined. Often for these issues couples or group psychotherapy is required. Sexual education regarding normal male sexual response cycles and variability in sexual response and practices is an important component of therapy.

There are no pharmacological treatments for low sexual desire that have well-documented efficacy (12). Testosterone supplementation may be effective to treat men with low desire who have low testosterone levels or low levels of bioavailable testosterone (13). Due to potential side effects, testosterone levels should be monitored. Unless a psychiatrist is well versed in administration and the potential side effects of these medications referral to a practitioner who has this experience is recommended.

16.3.2. Female Sexual Interest/Arousal Disorder

16.3.2.1. Criteria and Prevalence

DSM-5 has combined aspects of both Hypoactive Sexual Desire Disorder and Female Sexual Arousal Disorder to create *Female Sexual Interest/Arousal Disorder*. The disorder applies when a women has either a lack of interest in sexual activity or an inability to attain or maintain arousal. The name change reflects the common experience that desire and (at least subjective) arousal highly overlap. In some women desire precedes arousal; in other women, desire follows arousal. There are inconsistencies in how desire is defined, with some focusing on sexual behavior as an indicator of desire, with some definitions focusing on spontaneous sexual thoughts/fantasies, and others emphasizing the responsive nature of women's desire. The word "desire" in Hypoactive Sexual Desire Disorder has been changed to "interest" as desire connotes a deficiency and often implies a biological urge. The phrase "…an adequate lubrication-swelling response of sexual excitement" in DSM-IV-TR Female Sexual Arousal Disorder has been eliminated because evidence suggests that increases in vaginal blood flow during exposure to sexual stimuli may be a relatively "automatic response," and one that women may or may not be aware of. Further, there is little evidence that women with a sexual arousal disorder have impaired genital response; lubrication may or may not co-occur with subjective arousal (14, 15). For instance, a large British study of women 18 to 70 found that 17% of the women reported problems with arousal that was not associated with vaginal dryness (16). This was also true of 5% of the women in the SWAN study (17). It is interesting to note that in women subjective feelings of arousal are poorly correlated with genital response. Women can report feeling sexually aroused without significant physiological changes and may have measurable physiologic changes without reporting subjective arousal.

16.3.2.2. Etiology

In an outstanding review of sexual desire and arousal disorders published in *The New England Journal of Medicine* in 2006, Basson discusses physiologic factors that may affect genital vasocongestion in women (15). In postmenopausal women, low estrogen levels and vaginal atrophy are associated with reduced levels of vaginal congestion when a woman is not receiving sexual stimulation. However, the percent increase in response to sexual stimuli is similar either in the presence of low or high estrogen levels (18). If there is sufficient stimulation even women with estrogen deficiency may become adequately lubricated. However, in about 40% of women vaginal atrophy does adversely affect sexual functioning and sexual response (19). There is a debate about the role of oral contraceptives in affecting sexual function. Oral contraceptives increase levels of sex binding globulin, which leads to reduced free testosterone levels that could affect sexual function (20). There has been a lot of debate over the role of low testosterone in contributing to female sexual arousal disorder and the use of testosterone in the treatment is quite controversial. However, no correlation has been found between sexual arousal and serum testosterone in large population studies of women (21). There are multiple medical issues that can contribute to arousal difficulties in women, including diseases such as multiple sclerosis, renal failure, and premature menopause by chemotherapy (15). Obviously psychological and psychiatric problems can affect sexual functioning. Significant stress or discord with a partner can contribute to difficulties with arousal.

16.3.2.3. Diagnosis

A history, physical examination, including a gynecological exam, and laboratory testing need to be done to rule out medical illnesses that may be contributing to female sexual interest/arousal disorder. A careful history needs to be taken regarding potential psychological and relationship issues that may be contributing to the problem. Ideally partners would be interviewed together, as well as individually in order to understand the relational issues. The Brief Index of Sexual Functioning

Inventory is a validated 21-item self-report inventory assessing sexual interest, activity, function, and satisfaction that can be used in this circumstance (22).

Vaginal photoplethysmography is a specialized vascular test for female sexual arousal (23). A tampon sized light source and detector instrument is used to record vaginal blood flow during sexual stimulation. Duplex Doppler ultrasonography, laser Doppler, and laser oximetry are other methods for assessing female genital blood flow. It is important to note that objective vascular tests have repeatedly shown a lack of correlation with subjective awareness of vaginal vasocongestion (23).

16.3.2.4. Treatment[1]

There are two excellent recent reviews of treatment of interest/arousal disorder in women by Basson (15) and Arlt (24). The latter focuses specifically on the use of testosterone in women. Basson concludes, "At the present time I would not recommend any pharmacotherapy pending the availability of more (and long-term) data in support of such treatment" (15). However, she does review the possible available therapies, including sildenafil, because of the involvement of nitric oxide in neurogenic vasodilatation during sexual arousal in women (15). In a small trial of women with genital arousal disorder some women reported improvement (25). However, in two larger trials in women with a combination of arousal and desire disorders there was no improvement in either desire, sensation, lubrication, or satisfaction (26). Sildenafil is off-label in women and since the teratogenic potential is unknown it can only be used in women with extreme caution.

Estrogen has been proposed as a possible treatment of low desire in women. The vaginal estradiol ring, which delivers local low-dose estrogen to the vagina seems to be a safe treatment for women with dyspareunia or lack of lubrication secondary to postmenopausal vaginal atrophy (15). The Women's Health Initiative Trial raises important questions about the safety of systemic estrogen for this purpose.

There has been much discussion and many publications regarding the use of androgen therapies to treat low desire in women. In a comprehensive review published in the *European Journal of Endocrinology*, Arlt (24) concluded:

1. Androgen replacement seems to be a promising option for the treatment of women with established causes of severe androgen deficiency, including surgical menopause or adrenal insufficiency if they concurrently suffer from symptoms of impaired mood and libido.
2. Importantly, impairment of libido is multifactorial in origin and in the majority of cases is not associated with androgen deficiency.
3. It is important to acknowledge that physiological menopause in women with intact ovaries is not associated with a sudden loss of androgen synthesis unlike the steep drop in ovarian estrogen production; therefore, postmenopausal women do not routinely require androgen replacement.
4. The slow, age-associated decline in Dehydroepiandrosterone (DHEA) and DHEA sulfate may well represent a physiological, protective mechanism, e.g., preventing increased sex steroid action in breast tissue.
5. More long-term studies in larger cohorts of women with severe androgen deficiency are needed comprehensively to assess both potential beneficial and adverse effects.

Basson and Brotto (25) also agree that low dose testosterone patch applied twice weekly administered concurrently with estrogen is helpful for women who have undergone surgically-induced menopause; however, one must be concerned about the potential androgenic side effects, including hirsutism, acne, insulin resistance that may predispose to metabolic syndrome, and a potential decrease in the high density lipoprotein (HDL) cholesterol level.

A non-pharmacologic agent that can be used to treat arousal disorder in women is the Eros-CTD (11). This is an FDA approved device designed to improve arousal by increasing blood flow to the clitoris. The woman applies a small plastic cup to the clitoris and engages a battery operated vacuum pump several times a week. Studies show no adverse events and improvement for most users in sensation, lubrication, and orgasm [reviewed in (11)].

16.3.3. Erectile Disorder

Erectile disorder applies to situations when a man is unable to attain or maintain an adequate erection. This can happen at the outset of a sexual encounter, while attempting to penetrate, or during thrusting. Some men are able to have an erection only during masturbation. If the man fails to have erections upon awakening or during masturbation, a medication side effect, a general medical condition, or a drug of abuse should be considered as a potential cause. To make the diagnosis of erectile

[1] Editor's comments: A new FDA-approved medication named Flibanserin has been introduced into the market for the treatment of female arousal disorder, recently.

disorder, there needs to be one of three problems with either attaining an erection, maintaining an erection, or absence of rigidity in erection that impact negatively on sexual activity.

16.3.3.1. Prevalence

According to a review by Beutel et al. (27), the prevalence of erectile dysfunction varies according to age. It is about 2.3% in men 30 to 39 years old and up to 5.9% in 40 to 49 year olds. The reported range in 50 to 59 year olds is 2% up to 30.8% depending on the series, and 11% to 55% for those up to age 60. Reported prevalence for those over 70 ranges from 15% to 53% and 80 and above 64% to 76%.

16.3.3.2. Etiology

There are multiple medical problems that can account for organic causes of erectile dysfunction and these medical causes should be ruled out before assuming that there is a psychological basis for the disorder. The patient should be worked up for disorders such as hypertension, heart disease, diabetes mellitus, elevated cholesterol or other lipid levels, kidney disease, hypogonadism, and possible lower urinary tract infection (27). Many of the medications used to treat the previously mentioned disorders can cause erectile dysfunction, in particular the antihypertensives and serotonin reuptake inhibitors. Psychiatric disorders such as depression and anxiety can have a marked negative effect on erectile function. Use of substances, particularly narcotics, alcohol, and marijuana, are associated with erectile dysfunction. Finally, a history of surgeries, such as prostatectomy or rectal surgery may be associated with neurologic causes of erectile dysfunction.

16.3.3.3. Diagnostic Testing

The review article by Wespes et al. (28), summarizes the major specialized diagnostic testing for erectile dysfunction. The gold standard test is the nocturnal penis tumescence and rigidity (NPRT) test that should be administered on two specific nights using the RigiScan®. The RigiScan® is a portable device that is used to assess erectile rigidity at the base and the shaft of the penis during an erection, and the duration of the erection. This device is considered to be more accurate than the older snap gauge, which was made up of cellophane strips of known tensile strength that is attached to the penis with Velcro®. During an erection the cellophane strips break. Nocturnal penile tumescence monitoring is based on the assumptions that males without erectile difficulties or with exclusively psychogenic erectile difficulties attain full erections four to six times per night during rapid eye movement sleep. However, men who have a disturbance of REM sleep or disorders such as sleep apnea may have false positive tests.

Other vascular studies include intracavernous injection of a vasoactive drug to determine if there is vascular insufficiency responsible for the erectile dysfunction (28). If the test is inconclusive, a duplex ultrasound of the penile arteries can be obtained. If the duplex examination is abnormal, penile artery arteriogram and dynamic infusion of the cavernosometry and cavernosography should be performed in patients who may be candidates for reconstructive vascular surgery. Neurologic studies can also be done to test the integrity of the neurologic system, including bulbocavernosus reflex latency and nerve conduction studies (28).

16.3.3.4. Treatment

Treatment options fall into four basic categories (28). First, healthy lifestyle changes may help reduce the comorbidity of certain medical conditions. Second, addressing organic problems, such as hormonal abnormalities or changing medications to minimize side effects is a reasonable approach. Surgical interventions include revascularization procedures, particularly for young patients with pelvic trauma. Third, psychosexual counseling and therapy can be very useful to address non-organic causes of the disorder. Finally, oral pharmacotherapy can be an option.

There are now four approved phosphodiesterase type 5 (PDE5) inhibitors (28). Treatment with these medications causes increased arterial blood flow leading to smooth muscle relaxation, vasodilatation, and penile erection. Sildenafil, tadalafil, vardenafil, and avanafil are the four medications currently approved. Side effect profile and duration of action vary between the medications and these issues should be discussed thoroughly with the patient before selecting a medication. Side effects can include orthostatic hypotension, headache, flushing, dyspepsia, change in vision or muscle pain. PDE5 inhibitors are contraindicated with organic nitrates when used to treat angina and amyl nitrate ("poppers") taken as a recreational drug. Nonarteritic anterior ischemic optic neuropathy is a rare but serious side effect so patients who have had a previous but possible transient severe loss of vision should be referred to an ophthalmologist before PDE5 inhibitors are prescribed. These medications should only be administered by psychiatrists if they are willing to do the medical workup necessary to rule out

other potentially treatable causes of the erectile dysfunction and contraindications to taking PDE5 inhibitors. These medications are also used by psychiatrists for patients who have normal erectile function until they are treated with SSRIs and then psychiatrists will prescribe these to ameliorate the SSRI side effects. However, a careful history must be taken to ensure that the patient's erectile function was normal prior to the treatment with the SSRI to ensure that there are not other medical issues that need to be addressed.

Sublingual apomorphine is a centrally acting dopamine agonist that can be used to improve erectile function; however, its use has decreased markedly now that the PDE5 inhibitors are available (28). However, apomorphine may still be used in patients who take nitrates, as the PDE5 inhibitors are contraindicated for these patients. Topical pharmacotherapy includes treatment with vasoactive drugs including 2% nitroglycerine, 15% to 20% papaverine gel, and 2% minoxidil solution or gel (28). However, adverse events such as skin and glans erythema, burning sensation, allergic reactions can be associated with all of these and should be discussed carefully with the patient prior to administration. The partner can also experience hypotension and headache due to vaginal absorption of these topical agents.

Finally, vacuum constriction devices can be used. Use of these devices requires placement of a constricting ring around the root of the penis to retain blood within the copora (28). Then the vacuum device is placed over the penis and passively pulls blood into the copora cavernosa. Second line treatments include intracavernous injections of alprostadil, intraurethral prostaglandins E_1 administration and surgical implantation of a penile prosthesis (28).

16.3.4. Female Orgasmic Disorder

Female Orgasmic Disorder describes a situation wherein a woman has recurrent delay in or absence of orgasm. Because women vary widely in their orgasmic capacity and in the type or intensity of needed stimulation, the diagnosis should be given only when the orgasmic functioning is less than would be expected given those variables. DSM-5 has made changes to Female Orgasmic Disorder: "marked infrequency" of orgasms or "reduced intensity of orgasmic sensation" can both fulfill the diagnosis. The addition of "markedly reduced intensity of orgasmic sensation" reflects the fact that orgasm is not an "all or nothing" phenomenon and that diminished intensity of orgasm may be a problem for some women. The diagnosis relies on the clinician's judgment as what sort of orgasmic capacity a woman should have at a particular age and what kind of stimulation or sexual excitement phase should bring about orgasm. Because there are no clear-cut norms, the clinician is left to making arbitrary or subjective judgments.

16.3.4.1. Prevalence

Among women presenting to sex therapy clinics for treatment, the rate of anorgasmia ranges from 24 to 37% (6). In population-based studies approximately 15.4% of premenopausal and 34.7% of postmenopausal women report difficulty achieving orgasm (14). Single women seem to have a higher prevalence of the diagnosis compared to married or cohabitating women who are in a long-term committed relationship.

16.3.4.2. Assessment and Treatment

It is important, when treating female orgasmic disorder, to determine if an arousal disorder or lack of stimulation may be the cause of the orgasmic disorder. Women with acquired or secondary orgasmic dysfunction are more likely to have co-occurring psychiatric disorders than women with lifelong orgasmic disorder (6). When treating secondary or situational anorgasmia it is important to deal with the comorbid psychiatric disorders and address the emotional or relationship discord in order to have a favorable outcome. Women who are less likely to practice masturbation are also more likely to have orgasmic disorders (6). Masturbation training using either manual or vibrator-assisted stimulation and pubococcygeal muscle training seem to be most effective for treating lifelong or primary anorgasmia (7, 29, 30). However, achieving orgasm during masturbation does not necessarily guarantee the patient will be able to have orgasm during intercourse or when stimulated by a partner. There is much debate in the literature on female sexual response as to whether orgasm during intercourse without additional clitoral stimulation is a reasonable therapeutic goal for treatment of orgasmic disorder (29). Traditional sex therapy is also used in the treatment of anorgasmia. The overall success rate has been reported to be as high as 90% or better (7, 31).

16.3.5. Delayed Ejaculation

Delayed ejaculation applies when a man has a delay in or absence of orgasm. This disorder may take several forms. For some men, only certain types of stimulation lead to orgasm. Others may experience an orgasm but only after a prolonged and

intense sexual activity or stimulation. Delayed Ejaculation is the new DSM-5 name for DSM-IV-TR Male Orgasmic Disorder. The name change reflects current terminology in the field.

16.3.5.1. Prevalence

Delayed ejaculation has been reported by 46.2% of men and increases with age from 30% for men ages 50 to 59 to 54.9% in men ages 60 to 69, and 74.3% in men ages 70 to 80 (27). Inability to reach orgasm increased from 5% for 40 to 49 years olds up to 17% for 70 to 80 year olds in one study but another reported less than 5% for those under 60, 14% for those ages 60 to 69, and 34% for 70 to 79 year olds, and 55% for those above 80 (27).

16.3.5.2. Etiology

As with other types of sexual dysfunction it is important to rule out potential medical causes of delayed ejaculation. Potential causes and treatments are reviewed by Richardson et al. (32). Possible organic causes include diabetes mellitus, peripheral vascular disease, substance use, including alcohol, cigarettes, and many drugs of abuse, spinal cord injury, retroperitoneal surgery or trauma, and other neurologic disorders, such as multiple sclerosis. Prescription medications can be a major cause, including psychiatric medications, such as selective serotonin reuptake inhibitors, tricyclic antidepressants, and antipsychotic medications.

16.3.5.3. Treatment

Most of the publications on use of medications to treat delayed ejaculation related to management of the problem when it is secondary to the use of serotonin reuptake inhibitors (32). Amantadine, cycloheptadine, and yohimbine have all been suggested for treating delayed ejaculation caused by selective serotonin reuptake inhibitors (SSRIs). There have been some single blind and double blind studies of bupropion to treat SSRI-induced sexual dysfunction (33). Results have been mixed but this agent is often tried in clinical practice. Bethanechol has been reported to be effective in treating delayed ejaculation due to tricyclic antidepressants (34), and amantadine and buspirone were reported in a prospective study of depressed men and women with generalized sexual dysfunction to reverse the sexual dysfunction side effects of SSRIs, including retarded ejaculation (35–37).

Recommendations by sex therapists to treat retarded ejaculation often include masturbatory exercises with the partner, viewing of erotica during masturbation, increasing stimulation, and working with the couple to make sure there is adequate sex play prior to intercourse. Hypnosis has been suggested as a useful adjunct to treatment.

16.3.6. Premature (Early) Ejaculation

Early ejaculation is a condition in which a man ejaculates too quickly and with minimal stimulation before, on, or shortly after penetration and before he wishes to. Early ejaculation is more common in young men, in novel sexual situations, and in men who have had a substantial interval since last orgasm. DSM-5 changed the name from premature ejaculation disorder to avoid the use of an inaccurate and stigmatizing term.

16.3.6.1. Prevalence

In the review by Beutel et al. (27), 14% of men reported periodic to frequent premature ejaculation, and 7% reported an inability to have orgasm. Early ejaculation remains relatively constant with aging. It was reported to be 13% to 14% in men ages 40 to 59, and 17% to 18% in men ages 60 to 80.

16.3.6.2. Treatment

Pharmacotherapy for early/premature ejaculation most commonly takes advantage of the side effects of the selective serotonin reuptake inhibitors. There are reports in the literature of nearly all of the SSRIs being used to treat premature ejaculation, including paroxetine, fluoxetine, sertraline, and fluvoxamine [reviewed in (38)]. There are also reports of topical anesthetics, such as lidocaine and prilocaine preparations, and PDE5 inhibitors being used to treat early/premature ejaculation [reviewed in (38)]. Psychotherapeutic approaches that have been recommended include the use of distraction and decreasing excitement and stimulation to help to delay ejaculation; however, there is not good data to show long term efficacy of these techniques (38).

16.3.7. Genito-Pelvic Pain/Penetration Disorder

16.3.7.1. Definition and Prevalence

Genito-Pelvic Pain/Penetration Disorder applies when a person has pain or discomfort, muscular tightening, or fear about pain when having sexual intercourse. This DSM-5 disorder reflects a change from DSM-IV-TR wherein two distinct disorders – Dyspareunia and Vaginismus – were used to diagnose sexual pain disorders, both now subsumed under this new category. Dyspareunia and Vaginismus were unreliable diagnoses, and it was nearly impossible in many cases for clinicians to distinguish between the two.

Dyspareunia, defined as pain during intercourse, can occur in either men or women. The estimated prevalence in men is about 1 to 1.5% [reviewed by (7)]. In contrast about 10 to 15% of women report dyspareunia and the prevalence seems to be inversely related to age, with younger women complaining of fewer problems than older women [reviewed in (7, 39)]. The prevalence of pain during sexual activity for postmenopausal women may even be higher, with 34% stating they "sometimes" or "often" have pain during sexual activity (14).

16.3.7.2. Etiology

Physical factors that can cause Genito-Pelvic Pain/Penetration Disorder in women include hymeneal scarring, pelvic inflammatory disease, and vulvar vestibulitis (7). In men, Peyronie's disease, in which there is an extreme bend in the penis, can cause dyspareunia. Other causes in men include painful retraction of the foreskin and possible physical trauma to the genitalia (39). Psychological factors such as problems in the relationship with one's partner or a history of sexual abuse can also contribute to this disorder. As with other sexual dysfunction disorders, the organic cause of the original pain may not be the only factor for maintaining the problem and so an approach that examines both the physical and psychological aspects of the disorder are important.

16.3.7.3. Treatment

There are various medical and surgical procedures for Genito-Pelvic Pain/Penetration Disorder that can address the various organic causes of this disorder. However, since in many cases there has been a long history of discomfort or pain prior to medical or surgical intervention, there is often much residual anxiety and often decreased arousal in women (7). Cognitive behavioral therapy and sex therapy treatment have both been used to treat Genito-Pelvic Pain/Penetration Disorder.

16.3.8. Vaginismus

16.3.8.1. Prevalence

Vaginismus results from an involuntary spasm of the musculature of the lower third of the vagina. Approximately 12 to 17% of women who present for treatment have this complaint (7, 39). One of the questions about diagnosis of vaginismus is how to distinguish it from dyspareunia. Often it is difficult to determine if the vaginal contraction or pain itself prevent penetration. Any vaginal pain, including pain from dyspareunia, can be accompanied by muscular contractions and it is often difficult to determine if the contraction is involuntary (40).

16.3.8.2. Treatment

Physical treatment for vaginismus includes use of vaginal dilators. Patient starts with the smallest dilator of the set and gradually increases the size of the dilator used over the course of a number of weeks. Systematic desensitization procedures may include insertion of a finger or a tampon along with psychological treatment (7). As with most cases of sexual dysfunction, treatment seems to be more effective if both partners participate and are invested in treating the condition.

16.3.9. Sexual Aversion Disorder

16.3.9.1. Definition and Clinical Characteristics

Sexual aversion is characterized by extreme aversion to and avoidance of, all (or almost all) genital sexual contact with a sexual partner. Compared to the literature on hypoactive sexual desire disorder and the other sexual dysfunctions, there is comparatively little data published on sexual aversion disorder. Theoretically, the diagnosis can be made in either men or women but the publications on the topic focus on aversion in women. Most women are brought into treatment by their husbands and it has been

suggested that men with aversion disorder do not enter into relationships so they are not likely to come to the attention of health care professionals (41). Prevalence data are not available but researchers have reported on the behavioral features of the disorder. Women with sexual aversion disorder avoid expression of affection because this might cause their partner to interpret this as a sign of willingness to engage in sexual activity. They don't go to bed at the same time as their partners, are uncomfortable with nudity, are repulsed by their partner's touch, and dissociate during sexual activity (41). Interestingly, about half of the women with sexual aversion have normal desire. They may masturbate regularly and they may have average levels of sexual fantasy (41). There are no studies documenting the efficacy of treatment but individual or couples therapy is usually the recommended treatment though women may not tolerate the traditional sex therapy approaches (Table 16.1).

16.4. Gender Identity Disorders

The DSM-5 has two sets of criteria for gender identity disorder diagnoses, gender dysphoria in children and gender dysphoria in adolescents and adults.

In response to criticisms that the term "Gender Identity Disorder" was stigmatizing, it has been replaced in DSM-5 by *Gender Dysphoria*. In addition, the previous subtype pertaining to sexual attraction was eliminated, and a new subtype categorization that does not exclude individuals with a somatic disorder of sex development was introduced.

Gender Dysphoria is characterized by persistent cross-gender identification, discomfort with one's assigned sex, and clinically significant distress or impairment. The diagnosis may be problematic in children because of the child's inability to verbalize distress, and gender identification may be transient or developmentally related. In some, the distress may reflect parental disappointments (i.e., about the child's gender) rather than the child's internal distress. In adolescents or adults, the disturbance is manifested by symptoms such as stated desire to be the other gender, frequent passing as the other gender, desire to live as the other gender, and the conviction that the person has the typical feelings and reactions of the other gender.

There is significant debate in the transgendered community and among practitioners who provide services for transgendered individuals regarding whether gender dysphoria disorders are mental disorders. Those arguing against having gender dysphoria disorder in the DSM posit that it adds to social stigmatization of a normal variant of human gender expression. Others feel quite strongly that it is only because of the formal diagnosis that those with gender dysphoria disorder are able to access healthcare and health insurance coverage to provide benefits for psychological treatments, as well as hormone and sex reassignment services. Care of transgendered individuals has been positively affected by the development of standards of care for gender dysphoria disorders developed by the Harry Benjamin International Gender Dysphoria Association (42). These guidelines provide standards for assessment and treatment of gender identity disorder in children, adolescents, and adults and will be used as the basis of the discussion that follows.

16.4.1. Prevalence

It is estimated that approximately 1 in 11,900 males and 1 in 30,400 females would be eligible for the diagnosis of gender dysphoria (43). In some patients the intensity of the gender dysphoria fluctuates below and above clinical threshold. Genetic females can function in society in an androgynous state without drawing attention to themselves. It may be that some nonpatient male transvestite female impersonators and male and female homosexuals have a form of gender dysphoria.

Little is known about the course of gender dysphoria because of the lack of studies in the area; however, it is thought to be the case that most boys or girls who express gender dysphoria as children outgrow their wish to change sex or gender (43). In clinical practice, it is certainly the case that patients who initially aspire to gender change decide not to pursue hormonal or surgical sex reassignment for a multitude of reasons. Some patients decide that the social consequences of a gender change are not acceptable and settle for some intermediate state of gender and others wish to pursue hormonal and surgical sex reassignment (43).

16.4.2. Clinical Presentation

It is important to note that the majority of children who present with gender dysphoria do not go on to be transgendered adults (43). Commonly children and adolescents present stating that they desire to be the other sex, dressing in clothes of family members of the opposite sex, playing with games and toys usually associated with the opposite gender, and preferring playmates of the opposite gender. The disorder is more commonly diagnosed in boys than girls and boys can also complain about not liking their physical sex characteristics. The majority of children and adolescents with gender dysphoria do not become transsexual although research indicates that they may eventually become homosexual (43). Gender dysphoria in boys is more closely tied to later homosexuality than to the development of adult transsexualism. Retrospective studies of

male and female homosexuals are more likely to endorse cross-dressing in childhood and adolescence than in heterosexual individuals.

Often when adult transsexuals present for treatment they have been aware of the desire to alter their gender for many years and are very impatient to get started on hormones or have surgery immediately. They often exhibit a great deal of distress about their bodies, particularly primary and secondary sex characteristics, and they report the dissatisfaction since they were children or adolescents. They may have actually experimented with cross-dressing in a subtle or overt manner. Men may wear women's underwear so as to not have the cross-dressing apparent to others. They may have already selected a name of the desired gender and are quite anxious to proceed with the sex change.

16.4.3. Assessment

When seeing a patient with gender dysphoria it is important to address the differential diagnosis. Clearly in children and adolescents it is advisable to be accepting of their gender dysphoria but also acknowledge that this may not be a long-term process. A detailed discussion of the potential benefits and side effects of treatment in childhood and adolescence is beyond the scope of this chapter; however, can be found in the Harry Benjamin International Gender Dysphoria Association Standards of Care (42). Irreversible interventions, including any surgical intervention, should not be carried out prior to adulthood.

Differential diagnosis of gender dysphoria in adults is most difficult when distinguishing from transvestic fetishism and gender dysphoria, particularly if the patient presents stating that the cross-dressing is sexually arousing. Additionally, young male homosexuals with a history of stereotypically feminine interests or behaviors and possibly cross-dressing may be mistaken for patients with gender dysphoria.

16.4.4. Treatment

According to the Standards of Care, there are five elements to the clinical work of professionals with patients with gender dysphoria. They include diagnostic assessment, psychotherapy, real-life experience, hormone therapy, and surgical therapy. Psychiatrists who work with patients with gender dysphoria may appropriately carry out any of the following responsibilities (42).

1. Accurate diagnosis of the individual's gender dysphoria disorder.
2. Accurate diagnosis of comorbid psychiatric conditions and appropriate treatment of such conditions.
3. Counsel individuals about the range of treatment options and their implications.
4. Provide psychotherapy.
5. Ascertain eligibility and readiness for hormone or surgical therapy.
6. Make formal recommendations to medical and surgical colleagues.
7. Provide relevant patient history to referral sources in the form of a letter of recommendation.
8. Maintain professional relationships with others who can provide support to those interested in gender identity treatment of gender dysphoria.
9. Educate family members, employers, and institution about gender dysphoria.
10. Be available for follow up of patients who receive treatment of gender dysphoria.

Patients with gender dysphoria may select from a whole range of options to deal with their disorder. While some are comfortable with finding a middle ground, taking hormones but not having surgery or in the case of women, having mastectomy but not penile construction, others feel it is necessary to be as completely physically like the gender of choice as possible. For most patients with gender identity disorder a period of psychotherapy is required. Real-life experience in the gender of choice is considered critical according to the Standards of Care before proceeding to hormonal or surgical treatment (42). This involves dressing, presenting, and living as an individual of the gender of choice for a period of time prior to starting on hormones or obtaining surgery. The real-life experience is critical because the consequences of the sex change may be different from what the patient imagines them to be. These issues need to be addressed prior to irreversible physical changes being made. When the psychiatrist is fully assured that the individual is psychologically stable and prepared for the next phase of treatment it is appropriate for them to send letters of recommendation to the physician prescribing hormones or to a surgeon.

16.4.5. Hormone Therapy

Hormones should only be prescribed by a practitioner who is fully versed in the potential medical consequences and is attendant to the management of these consequences, such as changes in glucose tolerance and possible development of diabetes,

effects on cardiovascular disease, venous thromboembolic disease, liver abnormalities, hyper-prolactinemia, and osteoporosis. Programs following the Standards of Care make certain that the person receiving hormones be eighteen years of age, demonstrate knowledge of what hormones medically can and cannot do and their social benefits and risks, as well as the medical benefits and risks (42). The medical and social risks should not be minimized. The person must also either have a documented real-life experience of at least three months prior to administration of hormones or a period of psychotherapy of a duration specified by the mental health professional after the initial evaluation (usually a minimum of three months) (43).

16.4.6. Surgical Treatment

There is significant research and clinical evidence that sex reassignment surgery is effective and even medically indicated for the treatment of severe gender dysphoria (43). Eligibility for a surgical sex reassignment includes being of the legal age of majority, having twelve months of continuous hormone therapy, and twelve months of successful continuous full time real-life experience. Some programs also require participation in psychotherapy but this is not an absolute requirement for eligibility. Patients must demonstrate the knowledge of the cost required, the length of hospitalization, the likely complications, and the post-surgical rehabilitation requirements of the various surgical approaches and have been made aware of different competent surgeons to perform the surgery. They must also have demonstrated that they are making progress dealing with the psychosocial aspects in the transition, including their job, informing close family members, and they must be free of significant physical, mental health, or substance abuse problems that would make surgery contraindicated. Female patients may choose to have mastectomy and hysterectomy, including a salpingo-oophorectomy. They may also have vaginectomy although if the patient plans to have phalloplasty, vaginal tissue is often used for this operation. Patients may elect to have scrotoplasty, urethroplasty, or placement of testicular prostheses. Metoidioplasty is the construction of a microphallus and is an easier surgery than phalloplasty. Female-to-male patients must explore all of these options before electing to have surgery. Male-to-female patients may have a number of genital surgeries, including orchiectomy, penectomy, vaginoplasty, clitoroplasty, and labiaplasty. Frequently male-to-female patients elect to have breast augmentation surgery. Various types of facial plastic surgery may be requested. While there are some surgeries that may modify the voice, Standards of Care suggest that more follow up research needs to be done before this procedure becomes widespread (42).

16.5. Paraphilias and Compulsive Sexual Behavior

16.5.1. Paraphilias

Paraphilic disorders are characterized by the presence of recurrent, intense sexually arousing fantasies, sexual urges, or behaviors generally involving: 1) nonhuman subjects, 2) the suffering or humiliation of oneself or one's partner, or 3) children or non-consenting persons (Table 16.2). Individuals may differ on whether the paraphilic fantasies are obligatory for arousal or used only episodically. Because not all paraphilias are considered mental disorders, DSM-5 makes a distinction between paraphilias and Paraphilic Disorders. With *Paraphilic Disorder* a paraphilia causes distress or impairment to the individual, or entails harm, or risk of harm, to self or others. A paraphilia is a necessary but insufficient condition for having a Paraphilic Disorder. Having a paraphilia does not in and of itself automatically justify or require clinical intervention.

Although often discussed in a group, there is considerable debate about which of the paraphilic disorders, if any, share a common underlying etiology. In addition, there is also debate over whether certain paraphilic disorders (e.g., sexual sadism, sexual masochism, pedophilia) should even be considered psychiatric disorders (44, 45).

Table 16.2 Paraphilic disorders.

Exhibitionistic disorder	Exposing one's genitals to strangers
Fetishistic Disorder	Sexual excitement from non-living objects
Frotteuristic Disorder	Sexual excitement from rubbing against someone
Pedophilic Disorder	Sexual interest in prepubescent children
Sexual masochistic Disorder	Finding sexual excitement in being humiliated
Sexual sadistic Disorder	Finding sexual excitement in the humiliation of others
Transvestic fetishistic Disorder	Cross-dressing (in a heterosexual male)
Voyeuristic Disorder	Observing an unsuspecting person who is partially or completely naked or having sex

16.5.1.1. Prevalence

There have been no large epidemiological studies of paraphilic disorders, and so the rates in the general community are not known. Small nonclinical studies, however, suggest that paraphilic disorders may not be rare. One anonymous study of college students found that 7% would have sex with a child if they could be assured that they would not be found out (46). In a different study of male college students, 3% reported having been sexual with a girl under the age of 12 years, 42% had been voyeurs, 2% had exposed themselves, and 35% had engaged in frotteurism (47).

16.5.1.2. Clinical Characteristics

Paraphilic disorders appear to start by late adolescence, except pedophilia which has a mean age of onset in the mid or late 20s (48). Although paraphilic disorders for most individuals begin by young adulthood, they may in fact start at any age (49). The intensity of the urges, fantasies or behaviors can differ dramatically in severity between individuals. For example, some individuals may require the paraphilic fantasy or behavior for all sexual arousal, whereas others largely engage in ordinary sexual behavior with only a fleeting urge or fantasy about the paraphilia (50).

Paraphilic disorders, although present in females (51, 52), appear to be more common in males (50). Given the paucity of research on females with paraphilic disorders, it is still unclear whether gender influences the clinical characteristics of these disorders.

Co-occurring disorders are common in individuals with paraphilic disorders, but the lifetime rates of these disorders demonstrate a large range. Lifetime mood (31% to 71%), anxiety (19% to 64%), substance use (23% to 60%), impulse control (29% to 52%), attention deficit hyperactivity (36%), and any personality (60% to 68%) disorders appear commonly in individuals with paraphilic disorders (44, 49, 53, 54). Additionally, individuals with paraphilic disorders tend to have multiple paraphilic disorders (54–57).

16.5.1.3. Etiology

Although the biology of sexual functioning and hypersexuality has long been explored (58–60), the pathology of paraphilias has been less studied. Because the orbital frontal cortex is involved in impulse control, social cognition, decision making and emotional processing, it becomes a likely candidate for understanding paraphilic behaviors. In addition, the prefrontal cortex is also involved in acquiring moral and social knowledge, and impairments in understanding moral and social values (seen in many individuals with paraphilias) may underlie these behaviors.

Current information provides only pieces of a complex puzzle. For example, frontal striatal circuits have been implicated in Tourette's disorder. Because individuals with Tourette's appear to have high rates of exhibitionism (61), these circuits may be a particularly important area for research. Pedophilia has been associated with a case of an orbitofrontal tumor, which resolved once the tumor was removed (62). A neuropsychological study of 4 individuals with pedophilia suggests that a striato-thalamo-cortical circuit may be involved in the pathophysiology of some cases of pedophilia (63).

Several neurotransmitters play a role in sexual functioning and motivation, and dysregulation of these neurotransmitters (serotonin, dopamine, norepinephrine) has been hypothesized to underlie paraphilic behaviors (64, 65). In addition, neuropeptides (e.g., gonadotropin-releasing hormone, thyroid-releasing hormone, and corticotrophin-releasing hormone), and the effects of these neuropeptides on hormones, have also been suggested as contributors to paraphilic behaviors (58). Even though several of the paraphilias combine elements of aggression and sexuality, no differences in circulating testosterone have been consistently found between sexual offenders and nonoffenders (66).

Animal models may hold some answers to etiology as pedophilia and exhibitionism have been reported in many species (67). Male gorillas may focus sexual attention on adolescent females when thwarted in attempts to mount an adult female. Male chimpanzees expose their erect penises to females as an initiating behavior leading to coitus (67).

Multiple psychological models have also been proposed for the possible etiology of paraphilic disorders. Behavioral models hypothesize that early conditioning to sexually deviant behavior results in the development of a paraphilic disorder (68). Social learning models suggest that lack of parental care, physical punishment, and frequent sexual activity within the family may predispose children to offending (69). Additionally, an addiction model has hypothesized that deviant sexual behavior acts as a drug substitute (66). Although these various models have served as paradigms to develop treatment approaches, they lack empirical evidence. How these various models interact with the various neurobiological theories has yet to be delineated.

Although various theories provide clues to the pathophysiology of paraphilic disorders, the etiology of these behaviors is most likely multifactorial (genetic, biological, developmental, social). In addition, multiple neurobiological and psychosocial dysfunctions might result in the behaviors diagnosed as paraphilias. Even among individuals with specific paraphilic disorders, there may be heterogeneity in their neurobiology. More comprehensive information of paraphilias, such as that

which could be gleaned from studies of genetics and neuroimaging, has significant potential in advancing our understanding of the etiology of these complex behaviors.

16.5.1.4. Treatment

16.5.1.4.1. Psychosocial Treatments

Cognitive behavioral therapy comprised of reducing deviant arousal and increasing appropriate arousal (e.g., desensitization, reconditioning techniques), improving ability to interact socially (e.g., social skills training, anger management), increasing victim awareness and empathy (e.g., role playing), correcting cognitive errors that allow rationalization of behavior (e.g., cognitive restructuring), and relapse prevention have demonstrated efficacy in reducing recidivism (70–72). Studies assessing this treatment approach, however, have generally focused on sex offenders, regardless of specific paraphilic disorder, and have included short treatment durations, and the studies have failed to use a no-treatment control group for comparison.

16.5.1.4.2. Pharmacotherapy

Although no consistent findings regarding testosterone levels among individuals with paraphilic disorders has been found, pharmacological agents (e.g., medroxyprogesterone acetate, cyproterone acetate) that reduce testosterone levels, via increasing testosterone reductase activity, have been used to reduce sexual urges and behaviors (73). Although promising in case reports and case series, there have been no double-blind controlled studies examining their efficacy. Similarly, case reports suggest that synthetic analogues of gonadotropin-releasing hormones reduce sexual urges and behavior in men with paraphilias by inhibiting secretion of naturally occurring gonadotropins and thereby reduce circulating levels of testosterone (74–76).

Serotonin reuptake inhibitors, pharmacologic agents that have anti-obsessional effects, have also shown promise in case reports in reducing paraphilia urges and behaviors. These medications have shown benefit for exhibitionism (77, 78), fetishism (78), sexual masochism (78), transvestic fetishism (78), and voyeurism (77, 79). There is yet no evidence that SSRIs differ in efficacy. No double-blind trials of SSRI medication have been conducted in individuals with paraphilias. When using these medications one has to be particularly careful about the anorgasmia or delayed orgasm side effect, as patients with paraphilias may find delayed orgasm actually increasing their need for intensity of stimuli during masturbation and therefore prolonging the amount of time spent engaged in masturbating to paraphilic fantasies, on the internet viewing pornography or engaged in paraphilic behavior.

16.5.2. Hypersexuality/Compulsive Sexual Behavior (Sexual Disorder NOS)

Although not recognized by the DSM-5, hypersexuality or compulsive sexual behavior is frequently discussed in the medical literature. This sexual behavior goes by a variety of names. These include hypersexuality, compulsive sexual behavior (CSB), sexual addiction, sexual compulsivity, and paraphilia-related disorder. In older literature terms such as perversion, nymphomania, Don Juanism, and hyper-eroticism have been used. A number of authors have proposed diagnostic criteria for this disorder and most are patterned after the criteria of the paraphilias (80–82). Salient features include recurrent and intense normophilic (as opposed to paraphilic) sexually arousing fantasies, sexual urges and behaviors which cause clinically significant distress in social, occupational, or other important areas of functioning. The hypersexuality must not be due to other medical conditions, substance use disorder, attributable to another Axis I disorder or developmental disorder, and must take into account norms of gender, sexual orientation, and sociocultural groups (83). Numerous behaviors have been described of those exhibiting compulsive sexual behavior, including compulsive cruising, multiple partners, compulsive masturbation, compulsive sexuality in a relationship, pornography dependence, telephone sex dependence, and cybersex dependence (83, 84).

Hyperactive sexual desire or hypersexual behavior is related to compulsive sexual behavior. Data published by Kafka (85) indicates that many of the men who present with this disorder have an average total sexual outlet (TSO) of greater than seven times per week. Total sexual outlet is defined as any sexual activity leading to orgasm, whether it be activity with a partner or masturbation behaviors. Previous publications indicate that the average TSO for adult males is 0.5 to 3 times per week, and in all the studies, a TSO of 7 or greater appears to be in the upper 3% to 8% of males (86, 87). Kafka (88) demonstrated that patients with CSB and those with paraphilias both exhibit hypersexual behavior at the same rates. In a sample of 206 males with paraphilias or CSB, 89% had a TSO of greater than 5, and 76% had a TSO of greater than 7. In this sample the age of onset of CSB was 18.7 years, with a range of 7 to 46 years. The average duration of time before the patient sought treatment was approximately 12 years.

16.5.2.1. Prevalence

There are no epidemiologic studies of the prevalence of CSB. However, Grant et al., (89) reported that 6.5% of 204 consecutive patients admitted to two inpatient psychiatry wards met criteria for CSB on a structured interview. Others have estimated the prevalence to be about 5% (90, 91). Clinical and research data indicates that CSB is predominately a male disorder. In different samples, 78% to 91% of those presenting for research studies or clinical treatment were male (90). Patients tend to present for treatment in their late thirties to early forties and come from a variety of socioeconomic backgrounds. In clinical practice, compulsive masturbation with use of internet, print, or phone pornography tends to be the most common presentation. Often male patients come in for treatment when their wife or significant other discovers and becomes disturbed by their behavior. With regard to Axis I comorbidity, mood disorders and anxiety disorders are common (91). Substance use disorders also present more frequently in those with CSB than in the general population. Patients often report strong urges to engage in the behavior, being preoccupied by thoughts and urges, attempting to resist the behavior.

16.5.2.2. Etiology

There are many theories regarding the etiology of CSB but no substantive research in the area. There are those that see the behavior as similar to addictive behavior and posit that the mechanism of drug and sexual addiction are similar (92, 93). Others see the disorders as being a type of paraphilia and assume that the etiology while unknown is similar to that of the paraphilias (94). To the extent that CSB is related to paraphilias the discussion above regarding the etiology of the paraphilias can also apply to compulsive sexual behavior. Others see CSB as a way to cope with anxiety and/or dysphoric mood (95). Atypical impulsivity (96) and hypersexuality (97) have also been suggested as causes. Our group has suggested that CSB is an urge-driven behavior and suggests that the basis of the urges and lack of frontal control over the urges that leads to CSB is similar to the abnormalities that lead to pathological gambling and other impulse control disorders (98, 99). There are multiple case reports in the literature of individuals with head injuries that develop hypersexual behavior. The majority of these lesions are in the frontal and temporal lobes (100–103).

16.5.2.3. Treatment

There is only one published placebo-controlled trial of citalopram for the treatment of compulsive sexual behavior (104). Treatment with citalopram leads to decreases in sexual desire/drive, frequency of masturbation and use of pornography (104). Both the placebo and treatment groups showed reduced sexual risk and the reduction did not differ between groups. There are multiple reports of case studies and case series of various medications suggesting efficacy in the treatment of CSB. Multiple authors have suggested selective serotonin reuptake inhibitors (SSRI) such as fluoxetine, sertraline, and paroxetine can decrease compulsive sexual behavior (105–113). The SSRI may work by decreasing urges to engage in the behavior and decreasing preoccupation. There are also case reports of tricyclic antidepressants (114) and buspirone (115, 116) being effective to help decrease anxiety and frequency of problematic behavior in those with CSB. Nefazodone has been recommended as an alternative to SSRIs since it is not as likely to cause sexual dysfunction (117) but the recent "black box" warnings about liver dysfunction have decreased the use of this medication. Earlier case reports indicate lithium carbonate and carbamazepine may be helpful in treating CSB (108, 118, 119). Atypical antipsychotic agents have been suggested as an option (106), particularly in those with any Axis I or II psychotic symptoms in addition to their compulsive sexual behavior. More recently naltrexone has been recommended for the treatment of behavioral addiction, including compulsive sexual behavior (120). High doses of 100 to 150 mg are generally needed. The use of non-steroidals is contraindicated with high dose naltrexone and liver functions must be followed carefully (121).

16.5.3. Conclusions

Paraphilic disorders and compulsive sexual behavior have historically received relatively little attention from clinicians and researchers. As such, our understanding of the basic features of these disorders is relatively primitive. Future research investigating the neurobiology of paraphilic disorders and CSB holds significant promise in advancing prevention and treatment strategies. The systematic study of treatment efficacy and tolerability is in its infancy. With no studies published yet that even approximate a controlled efficacy trial, it is not possible to make treatment recommendations. Nonetheless, specific drug and behavioral therapies appear to offer promise for the effective treatment of paraphilias and CSB. Heterogeneity of treatment samples may also complicate identification of effective treatments. At present, issues such as which medication to use and for whom, or the duration of pharmacotherapy or CBT cannot be sufficiently addressed with the available data.

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17
Other Psychiatric Syndromes: Adjustment Disorder, Factitious Disorder, Illicit Steroid Abuse, Cultural Syndromes

William R. Yates, M.D.

Abstract Many psychiatric textbooks omit less common, yet important, clinical topics in the medical basis of psychiatry. This chapter covers four such additional areas: adjustment disorder, factitious disorder, illicit anabolic steroid abuse, and special psychiatric syndromes identified by eponyms or cultural ties.

Keywords Adjustment disorder • Factitious disorder • Anabolic steroid abuse

Adjustment disorder and factitious disorder are important, but understudied, psychiatric syndromes. Adjustment disorder is one of the most common mental disorders in primary care, the emergency room and in medical and psychiatric inpatient populations. Factitious disorder requires collaborative care between medical and psychiatric specialists for accurate assessment and management. Increased use of illicit anabolic steroids and other performance enhancing drugs has both medical and psychiatric implications. Finally, knowledge of psychiatric eponyms and cultural syndromes reminds clinicians of the importance of history and cultural awareness in the medical basis of psychiatry.

17.1. Adjustment Disorder

17.1.1. Definition

The DSM-5 criteria for adjustment disorder deal with development of various behavioral symptoms (i.e., depression, anxiety, etc.) in response to obvious stressors which are unusually severe and cause social impairment.

By definition, the distress and impairment must evolve within 3 months of the stressor. The adjustment disorder is classified as acute for symptoms lasting less than 6 months and chronic for symptoms lasting over six months. The disorder is transient, with resolution over time or with development into a more severe syndrome such as major depressive disorder (1).

The maladaptive reaction to a stressor is confirmed by either impairment in occupational or social functioning or symptoms that exceed a normal response. Additionally, the symptom complex must not meet criteria for any other specific psychiatric disorder. For example, a patient displaying a full major depressive disorder following a divorce is diagnosed with major depressive disorder and not with adjustment disorder with depressed mood. The role of the stressor in the major depressive disorder is noted with a reference to the psychosocial stressor severity rating on Axis IV.

W.R. Yates, M.D. (✉)
Professor of Research, Department of Psychiatry, University of Oklahoma College of Medicine, Tulsa, OK, USA
e-mail: WRY888@gmail.com

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TABLE 17.1 Prevalence estimates of adjustment disorder in various populations.

Category	*N*	Site	Contact	Prevalence (%)	Reference
Children	386	Community	Survey	4.2–7.6	[2]
Adolescent suicides	56	Urban	Postmortem	14	[3]
Suicide attempters	127	Inpatient	Consult	24.4	[4]
Gunshot wounds	260	Inpatient	Consult	10	[5]
Consultation series	1048	IP/OP	Consult	11.5	[6]
Geriatric	197	Nursing home	Consult	16	[7]
Psychiatric clinic	5573	Outpatient	Diagnostics	12.3	[8]
Psychiatric hospital	2699	Inpatient	Admissions	5	[9]
Bone marrow trans.	95	Outpatient	Survey	34.7	[10]
Adults	2512	Community	Survey	0.9–2.3	[11]

17.1.2. Epidemiology

The prevalence of adjustment disorder in various populations has been the subject of limited attention. This limited attention results from several factors. Standardized interviews and operationalized criteria are recent developments. Nevertheless, several studies in various populations exist (2–11). These studies suggest that adjustment disorder is a frequent clinical condition worthy of further study. A recent survey of general practitioners in Denmark found that depression and adjustment disorder ranked as the top two mental disorders in primary care combining to account for 51% of all mental disorder diagnoses (12). Several prevalence studies of adjustment disorder are summarized in Table 17.1.

17.1.3. Clinical Picture

The clinical profile of symptoms in adjustment disorder is quite variable and is related to the developmental level and age. Adolescents appear to be more likely to develop behavioral problems with acting-out symptoms. Adults appear more likely to respond in a maladaptive fashion with depressive and anxiety symptoms.

Generally, the clinical picture reflects mild to moderate distress in the context of significant psychosocial difficulties. Symptom severity is less than most other Axis 1 disorders. Nevertheless, the symptom severity in adjustment disorder is significant enough to distinguish this population from community samples free from psychiatric illness (8).

17.1.4. Illustrative Case

Mrs. K was a 64-year-old married white woman who was admitted to the coronary care unit for congestive heart failure and atrial fibrillation. The attending physician requested a psychiatric consultation for episodes of nervousness and anxiety.

Mrs. K reported persistent anxiety since being admitted to the hospital. She felt her symptoms stemmed from confinement to her hospital room. Her usual daily activities included plenty of action and movement. Being restricted to her room made her feel trapped and out of control. She had difficulty sleeping and felt keyed up with rumination about her physical condition.

The patient denied depressed mood. There was no history of past or current panic attacks. She denied obsessions, compulsions, or phobias. She did not drink alcohol. She had no major significant psychiatric history. She did undergo a brief trial of hypnosis after a divorce. There was no history of psychotropic medication use, psychiatric hospitalization, or suicide attempts. There was no family history of psychiatric disorder.

Her medications at the time of her psychiatric evaluation included sucralfate four times daily, warfarin 5 mg daily, sublingual nitroglycerin, furosemide 40 mg daily, captopril 37.5 mg three times daily, digoxin 0.125 mg daily, metoclopropamide 10 mg four times daily, and diazepam 5 mg every 6 hours prn. Mrs. K reported that the diazepam relieved her anxiety symptoms, but she had received only one dose over the last 72 hours. Onset of her anxiety symptoms did not coincide with the initiation of any new medication during her hospital stay.

Laboratory and medical testing revealed normal thyroid function studies. Complete blood count, arterial blood gases, and general chemistry screen were within normal limits. Her electrocardiogram revealed atrial fibrillation.

On mental status examination, Mrs. K appeared well groomed and was dressed in a hospital gown. A handshake demonstrated the presence of perspiring palms. She appeared anxious in facial expression and bodily movements. She did not appear depressed. Her thoughts were logical and goal directed without a formal thought disorder. There were no hallucinations,

delusions, or suicidal or homicidal thoughts. Her insight and judgment were unimpaired. Cognitive testing revealed no abnormalities of orientation, memory, concentration, or comprehension.

The psychiatric consultant considered the following diagnoses in the differential diagnosis: generalized anxiety disorder, obsessive-compulsive personality disorder, organic anxiety syndrome secondary to medication, delirium, and adjustment disorder with anxious mood. Adjustment disorder with anxious mood was diagnosed after ruling out the other diagnostic considerations. Recommendations included a trial of diazepam 5 mg bid and an additional 5 mg prn during hospitalization. Continued diazepam treatment after discharge was felt unlikely to be necessary. A psychiatric nurse visited Mrs. K regularly during her hospitalization and provided relaxation exercises. The cardiology team was encouraged to allow ambulation and physical therapy as soon as medically possible to allow the patient to return to her active lifestyle.

The patient's anxiety responded well to the combination of diazepam and relaxation training. At discharge, the diazepam was tapered and discontinued. In a follow-up visit 3 weeks after discharge, the patient's anxiety symptoms had essentially resolved.

17.1.5. Clinical Course

Symptom duration of less than 6 months reflects a generally good prognosis for adjustment disorder. Outcome studies of adults with adjustment disorder have found over 70% without significant impairment or psychiatric illness 5 years after the index diagnosis (13). This follow-up study found that those with a psychiatric disorder were likely to have antisocial personality, alcoholism, or a major depressive disorder. However, the generally favorable prognosis is tempered by an estimated 4% suicide rate in this study population.

Presence of an adjustment disorder diagnosis has been linked to completed suicide in United States Army personnel (14). A Danish study estimated that a diagnosis of adjustment disorder at psychiatric treatment facilities increased the risk of later suicide by a factor of twelve (15).

Patients admitted to a psychiatric hospital with a diagnosis of adjustment disorder with depressed mood appear to have a more favorable prognosis than those with other mood disorders. Adjustment disorder in one study of inpatients predicted a lower rate of psychiatric hospital readmission (16).

The prognosis of adjustment disorder appears less optimistic in the adolescent population. Andreasen and Hoerick's study (13) found that only 44% of adolescents were well 5 years after an index diagnosis of adjustment disorder. The most frequent follow-up psychiatric diagnoses in the adolescent populations included major depressive disorder, antisocial personality disorder, alcoholism, drug abuse, schizophrenia, and bipolar disorder. The 5-year follow-up of adolescent adjustment disorder also found a 2% suicide rate. However, the process of suicidal ideation is generally shorter in adjustment disorder compared to other mood disorders (17).

One study of youth with new-onset insulin dependent diabetes mellitus found a high rate of new psychiatric disorders in a 5 year follow-up (18). Forty eight percent of those with adjustment disorder subjects had a new psychiatric illness diagnosed compared to only a 16% rate in controls.

Masterson (19) also documented the poor prognosis in adolescents with adjustment disorder. Sixty-two percent of adolescents displayed moderate to severe impairment 5 years after an index diagnosis. The prognosis for adjustment disorder in adolescents appears to be especially poor when there is a disturbance of conduct (20). Psychiatric comorbidity may significantly contribute to poor prognosis in children with adjustment disorder (21)

17.1.6. Etiology

The cause of adjustment disorder stems from the interaction between a stressor and the adaptive mechanisms of the individual. The type of stressor responsible for the initiation of an adjustment disorder can be quite variable and mimics the types of stressors commonly seen in everyday life. In a series of adult patients receiving psychiatric care with a diagnosis of adjustment disorder, the most common types of precipitants included marital problems, divorce or separation, a move to a new location, financial problems, and school or work problems (13). The type of stressor precipitating symptoms reflects the clinical setting of contact. For psychiatric consultations in the general hospital, a frequent precipitant is acute and chronic medical illness.

The severity of the stressor appears also to play a role in the etiology of adjustment disorder. The risk of developing psychiatric symptoms appears to increase with increased stressor severity. However, the response does need to meet the maladaptive and excessive responses criteria noted in the adjustment disorder.

The individual's pattern of response to stress has some stability over time. Therefore, individuals with previous maladaptive responses are more likely to display repeated maladaptive responses. The reason some individuals are more vulnerable

to stressors is not completely known. Genetic and environmental factors probably influence individual risks for maladaptive response to stressors (22).

One case-control study investigated the role of baseline temperament and character as risk for development of adjustment disorder (23). This study was limited to a sample of male Republic of Korea conscripts. However, individuals who developed an adjustment disorder in this group had higher measures of harm avoidance and lower measures of self-directedness, cooperativeness and self-transcendence. This study suggests some psychological features may reduce the risk of an adjustment disorder in response to a significant stressful life event.

Support for the validity of the adjustment disorder diagnosis is beginning to emerge in brain research. A quantitative EEG study of a series of subjects with adjustment disorder with depressed mood found significant differences compared to a series of subjects with major depressive disorder (24). Subjects with adjustment disorder with depressed mood showed lower levels of EEG absolute power and coherence disruption compared to those with major depressive disorder. This finding is consistent with adjustment disorder with depressed mood being an important but less severe form of mood disorder.

17.1.7. Differential Diagnosis

The differential diagnosis for adjustment disorder focuses on the primary complaint. For example, differential diagnoses in a patient with marked anxiety prior to a surgical procedure would include adjustment disorder with anxious mood, generalized anxiety, panic disorder, simple phobia, anxiety due to a general medical condition, or a mood, substance abuse, or personality disorder. Generally, it is best to begin the differential diagnosis with attention to the predominant symptom and include disorders likely to produce the target symptom in the differential diagnosis.

Adjustment disorder is not diagnosed when the target symptoms are only one instance of a pattern of overreaction. Personality disorders encompass behaviors or traits that are personal characteristics stable for long time periods. Under stress, these traits may increase target symptoms or behaviors similar to those of an adjustment disorder. The differentiation of adjustment disorder and personality disorder is difficult during time-limited assessments of new patients.

Another stress-related diagnostic category in DSM-5 is the category of psychological factors affecting other medical conditions. In this disorder, the focus of attention is worsening of a physical condition due to a psychosocial stressor. Adjustment disorder with physical complaints is diagnosed when no physical cause of the complaints is identified. In contrast, a patient with rheumatoid arthritis experiencing increased pain following the death of a relative exemplifies psychological factors affecting physical condition.

A final stress-related category in DSM-5 is the category posttraumatic stress disorder (PTSD). This category differs from adjustment disorder in several ways. In PTSD, the stressor must be of sufficient severity to be considered an “event that is outside the range of usual human experience and that would be markedly distressing to almost anyone” (1). Note that this category places a greater emphasis on the extreme nature of the stressor compared with the adjustment disorder. Additionally, in PTSD, the traumatic event must be persistently re-experienced with avoidance and arousal symptoms. With PTSD there is no limit on symptom duration. The onset of symptoms can be delayed for more than 6 months.

Mood or anxiety disorders are frequent differential diagnosis concerns in patients displaying symptoms related to an identifiable stressor. It is important to question for the presence of major depression, dysthymia, panic disorder, and generalized anxiety disorder in patients seen for conditions in which adjustment disorder is being considered. Clinical factors appear to distinguish adjustment disorder with depressed mood from major depression (25). In a general hospital psychiatry series, major depression was linked to older age, widowed marital status, and living alone (26). Psychosocial stressors can exacerbate nearly any chronic psychiatric disorder, and the resultant increase in symptoms may appear to be due to an adjustment disorder. The key to differential diagnosis between adjustment disorders and an anxiety or a mood disorder is to elicit sufficient information to confirm whether a full anxiety or mood disorder is present.

17.1.8. Treatment

Treatment recommendations for adjustment disorder are based primarily on clinical experience. Few treatment studies focus on adjustment disorder. Although the often transient nature of the condition suggests that treatment has limited importance, treatment can significantly reduce distress. Additionally, identification and treatment may prevent development of a more chronic condition.

Identification of the individual causes of adjustment reactions is the beginning of treatment planning. For patients demonstrating acute anxiety or depressive symptoms, it is beneficial to question the patient about the most distressing source of stress. This precipitating stressor may be a misunderstanding or an overestimation of danger or risk. Simple acknowledgment of the stressor sources, along with education and support, provides the basis for beginning intervention.

It is helpful to consider the individual's usual coping strategies for dealing with stressors. Facilitating the use of past successful strategies can prevent the need for new strategies. For example, allowing hospitalized patients to contact trusted friends, family, or clergy and discuss their condition and receive support may be quite beneficial.

Psychotherapy principles for adjustment disorder focus more on crisis-intervention principles than on a particular psychotherapy model. A BICEPS (brevity, immediacy, centrality, expectancy, proximity, and simplicity) model successfully limits the functional impairment following exposure to significant military stressors (27). This model uses a brief intervention approach beginning as soon as possible following stressor exposure. Patients receive notice that they are expected to return quickly to their previous level of function. The intervention occurs without transfer to another location. Attention focuses on symptom reduction without attention to underlying personality or neurotic issues.

This strategy has implications for general hospital patients experiencing adjustment disorders in the hospital setting. Symptom identification begins as soon as possible with brief intervention strategies following immediately after symptom identification. Treatment occurs on the medical ward rather than on transfer to the psychiatric unit. Physicians can encourage and expect quick symptom resolution. Psychotherapy strategies remain basic, using approaches such as relaxation training.

A Cochrane Review examined the all psychotherapy research trials in adjustment disorder (28). This review focused on the effect of interventions on facilitation of return to work. This is an important issue as work impairment is a key component of the burden in adjustment disorder. The review found limited support for both cognitive behavior therapy and problem solving therapy in reducing the level of work disability in adjustment disorder. The authors of the review noted guideline development for treatment of adjustment disorder is limited due to the paucity of studies and small number of participants in adjustment disorder.

Medication approaches for adjustment disorder target the primary presenting complaint (29). The majority of adjustment disorder diagnoses are sub-classified with anxious, depressed, or mixed emotional features. Many adjustment disorders respond to support and the passage of time-some more severe and persistent syndromes merit consideration for medication trials. Treatment studies have suggested adjustment disorder with depressed mood responds as well as major depressive disorder to a trial of antidepressant medication (30). Patients in primary care suffering from adjustment disorders appear to respond well to antidepressant therapy (31). However, large placebo controlled studies of the efficacy of antidepressant treatment in adjustment disorder are generally lacking. A recent review noted insufficient evidence to support routine antidepressant use in adjustment disorder with depression or anxiety (32).

In the case study, short-term benzodiazepine administration alleviated a significant adjustment disorder with anxious mood. Benzodiazepines have the advantage of rapid onset of anxiolytic effect. Concern about long-term dependence and withdrawal symptoms minimizes when the course of treatment is 6 weeks or less. Rational strategies for benzodiazepine use in adjustment disorder include alprazolam, 0.75 to 3 mg, in three divided doses, lorazepam, 1.5 to 6 mg, in three divided doses, clonazepam 0.5 to 1 mg in two divided doses, or diazepam, 10 to 30 mg, in a single or divided dose. Doses can be titrated to the symptom level. In hospitalized patients, it is better to use regularly scheduled administration rather than rely on an as-needed or prn administration schedule. Physicians should notify patients that the medication is for short-term use and that the development of tolerance and dependence will be medically monitored.

17.1.9. Prevention

Adjustment disorders in the medical setting often arise out of fear or anxiety about medical illnesses, hospitalization, and medical procedures. Miscommunication between medical personnel and the hospitalized patient can contribute to the development of adjustment disorders. Clear communication about the diagnosis, prognosis, and treatment plan can prevent significant adjustment disorder problems. Physicians, nurses, and ancillary medical staff efforts at education and support for the acutely and chronically hospitalized patient are important. Anticipatory education decreases adjustment symptomatology and increases patient satisfaction with medical care.

17.2. Factitious Disorder

The voluntary production of physical or psychological symptoms or signs of illness represents the core for disorders classified as factitious disorders. The DSM-5 (1) classifies factitious disorder under the Somatic Symptom and Related Disorders. Two types of factitious disorder are listed: factitious disorder imposed on self and factitious disorder imposed on another.

The main feature of factitious disorder is the production of physical or psychological symptoms deceptively and in the absence of real illness. Production of symptoms occurs without regards to obvious external incentives.

Factitious disorder is another problem encountered in the hospital setting. Although much less common than adjustment disorder, factitious disorder presents a significant challenge for medical physicians and psychiatric consultants. Along with the challenge of documenting the voluntary production of symptoms, factitious disorder patients often evoke strong negative emotional responses in members of the health care team. The management of factitious disorder also adds to the challenging character of these disorders.

17.2.1. Definition

False clinical presentation with deceptive physical signs and symptoms is the type of factitious disorder historically known as Munchausen syndrome (33). The essential features of Munchausen's syndrome include pseudologica fantastica (pathologic lying), peregrination (traveling or wandering), and recurrent feigned or simulated illness. By definition, the physical symptoms or signs in factitious disorder are intentionally produced or feigned. The motive for this symptom production is a "psychological need to assume the sick role." Motivation by an obvious external incentive is absent. By definition, the symptoms cannot occur exclusively as part of another major mental disorder.

Another category in DSM-5 is factitious disorder with predominantly psychological signs or symptoms. The definition of this disorder is identical to that for factitious disorder with physical symptoms except for the psychological character of the intentional symptom. Factitious disorder with psychological signs or symptoms has less clinical description with mixed acceptance by psychiatrists. Some have suggested that this disorder is not a valid diagnostic entity because of unresolved issues in motivation, inclusion and exclusion criteria and outcome (34).

A form of factitious disorder in childhood exists. Referred to as Munchausen syndrome by proxy, this clinical disorder involves a parent-child interaction. For this disorder, parents fabricate symptoms or signs of illness in their children to maintain their child in a sick role. Various presentations in the pediatric setting exist (35). Parents who simulate illness in their children, commonly have a personal history of somatoform disorders and factitious disorder (36)

A recently discovered variant of factitious disorder is Munchausen by internet (37). Munchausen or factitious disorder by internet is the simulation of illness in social media forums such as on Facebook, Twitter or specific disease internet discussion forums. Individuals simulating illness in social media may be doing it to receive support and attention. Others may simulate illness on the internet to disrupt or belittle social groups. Very little research on individuals with factitious disorder by internet exists, but initial studies suggest similar features to those with factitious disorder in the healthcare setting.

17.2.2. Epidemiology

No community information exists for the general population prevalence of this disorder. Most estimates of the prevalence of this disorder originate from hospital and psychiatry consultation series. Table 17.2 notes the prevalence findings for factitious disorder in the medical setting.

17.2.3. Clinical Picture

The presenting clinical sign or symptom for factitious disorder can be quite variable. Despite this variability, certain symptoms encourage aggressive pursuit of factitious disorder in the medical differential diagnosis. These high-risk situations include recurrent skin infection, especially with fecal flora contamination; recurrent unexplained hypogylcemia in diabetics and others with access to insulin; unexplained bruises or dermatologic conditions; fever of unknown origin; and surreptitious use of prescribed and over-the-counter medication. Particular medical diagnoses such as cancer have been the focus of feigned illness. Predictably as new conditions arise and become more prevalent, factitious variants arise. For example, recent reports of factitious AIDS have developed (39). Feigned psychosis and feigned posttraumatic stress disorders exemplify factitious disorder with psychological symptoms (40, 41).

TABLE 17.2 Prevalence of factitious disorder in treatment populations.

Category	*N*	Site	Contact	Prevalence (%)	Reference
Teaching hospital	1361	Inpatient	Consult	1	[44]
Fever of unknown origin	343	Inpatient	Referral	9.3	[48]
Psychotic disorder	219	Inpatient	Series	4.2	[40]
Physician survey	105	Inpatient	Practice	1.3	[38]

In Munchausen syndrome by proxy, several similarities exist compared with adult factitious disorder (35). Common fabricated signs included bleeding, neurologic problems, rashes, glycosuria, and fever. Medical occupations are frequently noted in the mothers of these children, similar to the adult factitious disorder series.

17.2.4. Illustrative Case

Ms L was a 20-year-old single unemployed woman seen by her primary-care physician for recurrent right leg swelling. The recurrent swelling had occurred over a period of 18 months, resulting in several hospitalizations for "thrombophlebitis." The patient was taking anticoagulants. Despite anticoagulant therapy, the right leg continued to be intermittently swollen. The swelling resolved with elevation, rest, and compression stockings.

At one point during the patient's illness, while she was taking anticoagulants, an acute gastrointestinal bleed occurred. Bleeding resulted in anemia (hemoglobin level 5 mg/dl). The patient's prothrombin time was in the therapeutic range prior to the acute bleed. However, at the time of the acute bleed, the prothrombin time was elevated to greater than 30 seconds. Although the patient denied taking an excessive dose of warfarin, a pill count by the physician documented excessive daily dosing. The patient required transfusion to correct the anemia.

Ms L denied any significant psychological distress. She did not appear depressed or anxious or have any psychotic symptoms. She did not respond to the intermittent swelling with anxiety or increased concern about her condition. There was no previous psychiatric history. Ms L was an only child who lived at home with her parents. Her mother had been somewhat overbearing and dominant, to the point of completing all the patient's high school homework and paper assignments. Following graduation from high school, Ms L briefly attended a secretarial training course at a school 65 miles from home. She was unable to complete the course because of her recurrent leg difficulties. When her leg became intermittently worse, Ms L received care by her mother. Her mother constantly checked her condition and provided assistance with daily cares.

During one acute swelling episode, the patient presented to the primary-care physician's office. A physical examination was done in the usual fashion with the patient gowned. However, further examination of the proximal right leg revealed a half-inch-deep circumferential tourniquet mark.

Ms L was confronted. Her physician noted the voluntary production of leg swelling and offered to arrange a psychiatric evaluation. She was not punished or humiliated for her behavior. She refused psychiatric referral and left the physician's office without returning for any scheduled follow-up appointments.

Ms L's primary-care physician called her mother to determine the reason for noncompliance with recommendations for follow-up. She reported that Ms L had transferred her care to another physician in a town 25 miles away. Additionally, she later began work at the new physician's office as a medical transcriptionist.

17.2.5. Clinical Course

Separating factitious disorder into those with a Munchausen syndrome and those without defines two different prognostic groups. Munchausen syndrome has a very poor prognosis, with only one case report of successful treatment (42). Factitious disorder without a Munchausen's syndrome appears to have a better prognosis. Good prognosis correlates with patients who also have a major depressive disorder. Combined medical and psychiatric management also decreases the morbidity of the disorder.

Ten patients with factitious disorder with hypoglycemia have been the subject of an outcome study (43). Following identification of surreptitious insulin use, confrontation, and psychiatric treatment, only three patients showed complete resolution of their condition. Remarkably, two patients died during follow-up, presumably due to self-induced hypoglycemia.

The outcome of factitious disorder with psychological symptoms has received limited attention. In the study by Pope et al. (40) of factitious disorder with psychological symptoms, the outcome was poor. Nine patients were followed for 4 to 7 years. One had committed suicide. Seven of the remaining eight had significant histories of frequent hospitalizations. Factitious disorder with psychosis predicted a poorer outcome than true psychoses such as schizophrenia or mania.

Nineteen children with Munchausen syndrome by proxy received longitudinal study (35). Two died presumably from the effects of the factitious disorder. Eight children were removed from their parents with resolution of the feigned signs. Nine children remained with their parents after confrontation and with close supervision by social workers. Of these nine children, seven were completely well without symptoms on follow-up. Two children continued with frequent physician visits for minor complaints not considered harmful factitious problems.

17.2.6. Etiology

The etiology of factitious disorder is unknown. Most case series studies of factitious disorder show a female preponderance. A Mayo Clinic series of 93 subjects found 72% were women (43). The risk factor and personality studies in this disorder present some basis for theoretical attempts to define the etiology of the disorder. Because factitious disorder patients often have severe personality disorders, the role of personality development and deficits appears to be important. Case studies of factitious disorder have described significant drives for dependency. The production of serious medical signs and symptoms mobilizes a medical care structure that often places patients in a dependent relationship. Significant angry affect is documented in case studies of factitious disorder. Borderline personality disorder is common. Patients may receive satisfaction at deceiving their health care team and getting revenge for previous interpersonal conflicts.

A history of healthcare training or jobs is common in factitious disorder. The Mayo Clinic series found a healthcare background in 66% of women with factitious disorder but only in 12% of men. Individuals may use they medical knowledge as a gateway to presenting clinical signs and symptoms.

17.2.7. Differential Diagnosis

The primary difficulty in the differential diagnosis of factitious disorder is confirming the voluntary production of signs and symptoms. Many patients never demonstrate their factitious behavior to others. This lack of proof is often frustrating and leaves an element of diagnostic doubt.

Malingering constitutes a disorder similar to factitious disorder. Both disorders involve the voluntary production of symptoms. The primary distinction in malingering is evidence that the intent of the feigned symptoms or illness is to obtain an external incentive. This external incentive, or "secondary gain," is often financial reimbursement through disability or through liability damages. Non-monetary secondary gain also can be the motive for malingering. Non-monetary incentives include evasion of military duty, evasion of criminal charges or jail sentences, or becoming eligible for better living circumstances.

Personality disorders in the medical setting mimic some of the characteristics of factitious disorder. Borderline personality disorder patients often evoke some of the same anger and frustration in health care professionals as the factitious disorder patient. The self-mutilation behaviors found with borderline personality tend to be stereotypical-an example being repeated superficial lacerations over the forearm. Although such behavior is voluntary, the patient acknowledges the behavior as being self-inflicted.

True medical illnesses deserve careful consideration in presumed factitious disorder. Follow-up series of patients diagnosed with factitious disorder have included some who went on to have the factitious symptoms explained by medical disease (44).

Other somatoform disorders also involve unexplained somatic complaints. Somatization disorder differs from factitious disorder in the number of presenting complaints. Although multiple symptoms occur in factitious disorder, single symptoms or signs are more often the focus of attention. Somatization disorder symptoms are more likely to involve subjective pain complaints, while factitious disorder target symptoms and signs often involve objective signs, i.e., hypoglycemia, skin infection, or fever.

Psychiatric comorbidity presents an additional challenge in the assessment of factitious disorder. It is possible for the patient to have more than one psychiatric disorder including factitious disorder. Treatable psychiatric comorbid conditions should receive attention. Diagnoses in this category include mood disorders, anxiety disorders, psychotic disorders, psychiatric syndromes due to a medical condition, and substance abuse.

Careful consideration of the psychiatric and medical differential diagnoses of factitious disorder can lead to accurate diagnosis of the syndrome. Careful review of outside medical records including electronic health records may be key in coming to the correct diagnosis (45). Additionally, room surveillance in person or by video can provide relevant information.

17.2.8. Laboratory Tests

Laboratory test abnormalities may be crucial in the diagnosis of factitious disorder and Munchausen syndrome (46). This is particularly true with the surreptitious use of insulin. For patients without diabetes and without a medical cause for insulin treatment, the identification of insulin antibodies provides evidence of exogenous insulin use (47). Additionally, monitoring C-peptide levels during episodes of hypoglycemia also may confirm suspicions of surreptitious insulin use to produce factitious hypoglycemia.

Self-induced infections may produce cultures revealing multiple organisms commonly found in feces. For example, recurrent wound or skin infections growing such organisms as Escherichia coli, group D enterococcus, and Klebsiella is highly

suggestive of the use of feces to feign recurrent infections. However, fecal sources of bacteria are not the only source of possible infectious agents. Factitious infections from pure cultured bacteria also have been reported (48). Other pyogenic substances such as tetanus toxoid and milk proteins can produce a clinical picture of fever of unknown origin.

Bleeding and clotting factor studies provide assistance in evaluating the patient with unexplained bleeding problems. As in the case example, pill counting for factitious use of anticoagulants also can be helpful in confirmation of factitious disorder.

17.2.9. Treatment

The treatment of factitious disorder involves a coordinated medical and psychiatric assessment and treatment plan (49). Treatment of concurrent psychiatric disorders can assist in management. Factitious disorder is not a contraindication for somatic treatment of comorbid mood or anxiety disorders.

Early studies of the treatment and natural history of factitious disorder promoted confrontation of the patient as the key to beginning treatment. There is no consensus that confrontation, especially in a punitive fashion, is an effective treatment approach. There is no evidence that the patient must admit the self-injurious behavior has occurred in order for the clinical picture to improve.

After collecting sufficient evidence to confirm a factitious disorder diagnosis, a coordinated plan to notify the patient and provide follow-up care is needed. An example of a method of notifying the patient in a non-punitive fashion follows. This example is taken as a hypothetical approach to the illustrative case prior to the primary care physician scheduling psychiatric consultation.

Ms L, I would like to give you some information about my assessment and treatment recommendations. I know your leg swelling has caused you a significant amount of discomfort. I have tried my best to provide quality care for your condition. The observation of a tourniquet mark on your leg leads me to believe your behaviors have contributed to the problem. I understand behaviors like this have complex meanings but generally can be seen as a cry for help, for understanding, and for a needed more comprehensive evaluation of emotional factors involved in your life.

I will continue to care for your medical problems. I know that these behaviors have served some purpose for you, but as your physician, I must tell you they must now stop. I expect that with help and support you will be able to discontinue these behaviors. To provide assistance for you I will arrange for you to see a psychiatrist who will provide an expert evaluation and behavioral management plan for us. Together I believe we can provide you with a strategy to improve your physical and emotional health.

The role of psychotherapy in factitious disorder has received only minimal attention. The treatment is tailored to the individual patient and his or her individual psychiatric presentation. For patients with concurrent borderline personality disorder, cognitive therapy strategies for personality disorders exist (50). For the factitious disorder behaviors, behavioral management plans provide a method of intervention. Behavioral strategies should eliminate positive reinforcement in the home and hospital for the factitious behaviors. Behavioral strategies can allow the patient to minimize embarrassment and shame. Positive reinforcement for reducing factitious behaviors is also helpful. In Munchausen syndrome by proxy, the safety and health of the child are a priority for management. This syndrome is a form of child abuse. Notification of social services and the initiation of child abuse evaluations must begin when the syndrome becomes apparent.

17.3. Illicit Anabolic Steroid Use

Anabolic steroids (AS) are a group of natural and synthetic hormones with masculinizing as well as anabolic (tissue-building) properties. Illicit use of AS began with their discovery and synthesis in the 1940s. The illicit use of AS occurs primarily in the context of athletic competition-the goal of their use is to increase size, speed, and performance, thereby gaining a competitive edge. Illicit use is defined as use without a physicians' prescription. Illicit procurement of supplies occurs through black-market sources. Although the illicit use of AS compounds has a 50-year history, their use appears to be increasing and their effect on mental status is receiving increased attention. In 1990, AS were added to schedule III of prescription drugs covered by the Controlled Substances Act. This assignment has stimulated discussion of the addiction potential of the compounds. In this section, the scope, mental status effects, and addiction hypothesis for illicit AS use will be examined.

17.3.1. Epidemiology

Various population groups surveyed for the prevalence of illicit AS use, include high school and college students and participants in specific sports. The surveys have been predominantly self-report with limited reliability and validity testing. Despite

TABLE 17.3 Prevalence rates of AS use in various populations.

Category	*N*	Period	Males (%)	Females (%)	Reference
High school students (12th grade)	2350	Lifetime	5.0	0.5	[52]
High school students (12th grade)	3403	Lifetime	6.6	N/A	[53]
College athletes		12 months	6.2	0.6	[54]
Elite power lifters	45	Lifetime	55	N/A	[55]
Elite multiple-sport athletes	271	Lifetime	N/A	2	[56]
NCAA athlete survey	637	12 months	1.1*		[57]
Swedish adults between ages 14–64	13920	Lifetime	1.7	0.3	[58]

*Survey reported both genders combined.

this, the surveys suggest that AS use is common, begins frequently during the adolescent years, and is primarily a problem in men. Reviews of the epidemiology of AS use allow some general conclusions about the epidemiology of AS use (51). Table 17.3 summarizes several of the surveys with the best methodologies (52–58).

Anabolic steroid epidemiology is an important emerging issue in forensic psychiatry. A large urine sample study of individuals in police custody in Sweden found 33.5% of the samples being positive for anabolic steroids (59). Even 11.5% of inmates in prison tested positive demonstrating a significant contraband drug problem.

Yesalis (60) proposes that survey methods probably underestimate the prevalence rates of anabolic steroid use. Nonresponse bias is likely to play a role in underestimation due to the legal and sports sanctions attached to illicit use. The prevalence estimates of AS use double or triple when athletes estimate the use of AS in their peer group. This suggests that self-reported use of AS is a lower limit of the prevalence rates. Despite using this lower limit, estimates suggest that 250,000 adolescents in the United States are using or have used AS.

The growth of the internet appears to be a factor in anabolic steroid and other performance-enhancing drug epidemiology (61). A survey of websites focused on bodybuilding and steroids founds thousands of sites. Many promoted the use of anabolic steroids and had links to sources for mail-order performance enhancing drugs. Additionally, many of these sites minimized the health risk related to these compounds.

Several risk factors appear related to anabolic steroid use. Male gender predominates in this problem. Specific sports and specific positions within sports have higher rates of AS use.

Additional risk factors for anabolic steroid abuse and dependence include opiate abuse and dependence and cocaine abuse and dependence (62). Conduct disorder and antisocial personality disorder also appear to be risk factors (63)

One intriguing factor related to anabolic steroid risk is body-image disturbance. Individuals preoccupied with muscle size and shape appear at increased risk for initiation of anabolic steroids and later development of a dependence syndrome (63).

AS use typically occurs in 8- to 16-week cycles. AS use cycles are interspersed with periods of AS abstinence. The specific steroids ingested and durations of use are variable. The methods and patterns of use develop through user experience and are disseminated through word-of-mouth and underground publications (64). Typically, the AS use pattern involves the use of multiple compounds. Compounds can include oral as well as injectable drugs. Although AS compounds were used for therapeutic indications for many years, illicit users typically employ doses much higher than the therapeutic replacement dose. This high-dose pattern has limited the generalization of current knowledge. Medical and psychiatric effects of AS in therapeutic doses do not necessarily predict effects at supratherapeutic doses.

17.3.2. Psychiatric Effects

The apparent increased prevalence of AS use has brought the psychiatric effects of these compounds under attention. Early studies with testosterone and related steroids proposed an antidepressant effect for these compounds (65). These studies tended to be small and uncontrolled. AS treatment studies for depression decreased following the advent of tricyclic compounds. With the increased use of high-dose AS compounds in athletes, the adverse psychiatric effects of these compounds became more the focus of attention and research.

The types of psychiatric effects reported with high-dose AS use fall into three categories: mood syndromes, psychotic syndromes, and behavioral syndromes, especially the development of violent and aggressive behavior. Reviews of the psychological and behavioral aspects of use of the AS compounds describe complex psychiatric effects (66, 67). Some individuals using high doses experience minimal psychiatric effects, while others may develop full-blown mood or psychotic disorders. Individual vulnerability to the psychiatric effects may be influenced by past psychiatric history, family history of psychiatric disorder, type of steroid used, pattern of cycling, other psychoactive drug use, and other factors.

Mood syndromes of depression and mania have been reported in case series and controlled studies of AS use. During the cycling phase when AS is being used, a feeling of enhanced self-esteem and euphoria with increased energy and other mania-like features have been described (68). Depressive symptoms have been reported during on and off-cycle periods of use. Case reports of suicide in AS users also have been published (69, 70). The frequency that these mood syndromes meet criteria for a psychiatric diagnosis is unclear. Pope and Katz (71) argue for full affective syndromes in up to 12% of users, while other studies suggest that although psychiatric symptoms are common, the production of a syndrome characteristic of a full psychiatric disorder is rare (72, 73).

Psychotic symptoms reported with AS use have included ideas of reference, paranoid delusions, grandiose delusions, and visual and auditory hallucinations. These psychotic symptoms have been noted during cycles of AS use as well as during periods of withdrawal. AS compounds with a 17-alkylated structure appear to be most likely to induce psychotic symptoms. Compounds in this class include oxandrolone, methandrostenolone, and oxymethalone. In all cases reported, psychotic symptoms have responded to antipsychotic medication and remitted with prolonged abstinence from AS compounds.

The psychiatric effect of AS use best documented is aggressive behavior. The link of aggressiveness to AS use has the advantage of correlates in the nonhuman primates and other animal species. Numerous studies in mammalian species have documented the role of testosterone in the increase in aggressive behavior (74). Animal studies report that the aggressive effects of testosterone appear to be male-specific-this suggests that the presence or absence of testosterone during specific developmental periods controls later response to testosterone. Other social factors appear important in determining the pattern and severity of response in males exposed to exogenous AS. Rejeski et al. (75) studied a group of cynomolgus monkeys given equal amounts of exogenous testosterone. Increase in aggressive behaviors was seen primarily in monkeys that displayed significant aggression at baseline. This link may have significant human implications since there is some indication that AS users are more likely to have premorbid antisocial personality disorder (76).

The study of the aggressive effects of ASs in humans is limited primarily to observational studies and small experimental design studies. An AS-induced link to aggression has been used in court cases of AS-related assault and homicide. This legal approach has been labeled the "dumbbell defense." Case studies suggest that the violent behavior associated with AS use is primarily in response to some provocation, but the behavioral response is excessive and extremely deviant from what would be expected.

In addition to case reports, the psychometric effects of AS use have been the subject of investigation. Yates et al. (77) examined the role of AS use in a group of AS users and controls using the Buss-Durkee Hostility Inventory (BDHI) (78). This inventory measures several aspects of aggression and hostility. AS users reported elevated responses to scales measuring verbal aggression and direct and indirect aggression. Typical questions from elevated BDHI subscales illustrate differences between AS users and nonuser controls. (True responses scored positively.) For the assault scale, a typical question is: "Once in a while I cannot control my urge to harm others." For the indirect aggression subscale, a typical question is: "I can remember being so angry that I picked up the nearest thing and broke it." For the verbal aggression scale, a typical question is: "When I get mad, I say nasty things." These behavioral characteristics of AS users are likely to increase the risk for significant legal and interpersonal difficulties. Mean scores for AS users on the BDHI are higher than reported means for a group of psychiatric patients and a group of prison inmates (79, 80). The responses from AS users in this study showed some psychometric specificity. AS users had elevated scores on the aggression factor of the BDHI but not on a separate hostility factor.

Most studies of aggression in AS use have focused on retrospective designs, relying on the self-report of AS use to identify cases and controls. Two small prospective studies have monitored the effects of AS (81, 82). In one study, volunteers received an AS compound from the research team. Both studies confirm the aggressive effect of AS compounds. The Choi et al. study confirmed the relationship of AS use with the aggression subscale of the BDHI found in the Yates et al. study (77). Interestingly, a subject in the Su et al. study (82) asked to be placed in seclusion to prevent aggressive behaviors from getting out of control and resulting in harm to others.

One key study of the link between anabolic steroid use and violent behavior comes from the United States National Longitudinal Study of Adolescent Health (83). In this study of over 20,000 subjects, 2.6% of the male adolescents had a lifetime use of anabolic steroids. This group demonstrated higher rates of violent behavior even after controlling for significant potential confounding variables such as previous violent behavior and other drug use.

Significant questions about the exact role of AS in mental status and behavioral changes remain to be answered. Significant uncontrolled factors could affect the interaction of AS within individual users. Some of these factors include previous and family history of psychiatric disorder, individual personality traits and disorders, the concurrent effects of alcohol and other psychoactive agents, the effect of expectancy in response to use, and the environment in which mental status and behavioral changes occur.

Despite the limitations of the knowledge of the effects of AS use, several clinical implications appear warranted at this time. High-risk groups presenting with new-onset psychiatric disorders should have an AS use history obtained. Urinary AS

assays can be used to confirm the patient's history. Although AS use appears common, the majority of users have sub-clinical mental status effects. Despite this, documented significant clinical mental status and behavioral effects of AS use do appear to be present in a minority of users. Clinical suspicion regarding the mental status and behavioral effects of AS use in high-risk subjects is likely to lead to better understanding of the psychopharmacology of AS compounds.

One recent development related to the psychiatric effects of anabolic steroid use is attention to the cognitive function domain. A series of long-term anabolic steroid users completed a study of computerized neuropsychological function (84). Anabolic steroid users demonstrated significant impairment in visuospatial memory compared to controls. This study could not rule out visuospatial memory impairment as a risk factor for abuse rather than a consequence. Nevertheless, the study highlights the need for further attention to neuropsychological function in this population.

In addition to the psychiatric effects of AS compounds, the phenomenology of AS use compares in many ways with the phenomenology of DSM-IV psychoactive substance abuse and dependence. Similarities and differences in AS use compared with other drugs of abuse have implications about our understanding and treatment of AS use.

17.3.3. A New Drug of Abuse?

The underground pathway for the distribution of illicit steroids presents a law enforcement challenge. This distribution system has many similarities to illicit systems developed for drugs such as cocaine and heroin. AS compounds are often obtained from sources outside the United States and brought across the border with supplies assigned to dealers who distribute to individual users for monetary gain. Recognizing this pathway, in November of 1990 the U.S. Congress placed AS in schedule III of the Controlled Substances Act. This addition classifies AS in the same category as compounds such as acetaminophen with codeine. Illegal possession and distribution of these agents are now subject to felony arrest and prosecution.

Although AS compounds now are classified with other prescription psychoactive substances of abuse and dependence, the implication of this classification is unclear. The potential for AS use to develop into an uncontrolled habit with withdrawal and psychological and physical dependence is unknown and speculative. Kashkin and Kleber (85) have hypothesized that some individuals may be susceptible to an unrecognized sex steroid hormone-dependence disorder, and that such a disorder may be modulated through the relationship of AS to the opioid and aminergic neurotransmission network. The possible classification of AS as psychoactive substances of abuse and dependence has implications for the clinical assessment and treatment of AS users. The lines of evidence supporting this hypothesis as well as those not supporting it will be reviewed.

Support for the addiction hypothesis of ASs will be dependent on linking the phenomenology and biologic mechanisms of AS use with those of the use of existing psychoactive substances such as alcohol and cocaine. Table 17.4 presents some comparisons of these issues in addressing the AS hypothesis.

Several of the phenomenologic features of AS use mimic alcoholism and drug abuse. Use of AS compounds is primarily a male gender phenomenon. Although found in women, the male/female ratio for AS use appears to be about 10: 1. The ratio for AS users who could be considered dependent is unknown. Results from the National Institute of Mental Health's Epidemiologic Catchment Area (ECA) study suggest that the male/female ratio for alcohol abuse and dependence is 6:1 and for non-alcohol abuse and dependence is 1.6:1 (86). The age of onset for AS use is adolescence and early adulthood; this also

TABLE 17.4 Comparison of use of AS compounds with alcoholism and cocaine abuse phenomenology.

Comparison categories	Alcoholism	Cocaine abuse	AS use
Male gender predominant	Yes	Yes	Yes
Early age of onset	Yes	Yes	Yes
Linked to antisocial personality	Yes	Yes	Yes
DSM-IV abuse/dependence criteria	Yes	Yes	Yes
Polysubstance abuse common	Yes	Yes	Yes
Controlled Substance Act	No	Yes	Yes
Family history of abuse	Yes	Yes	Unknown
Used primarily for psychoactive effect	Yes	Yes	No
Seek treatment for discontinuation	Yes	Yes	Uncommon
Biologic mechanism/drug causes "high"	Yes	Yes	Unknown
Withdrawal symptoms/craving	Yes	Yes	Unknown
Animal model for self-administration	Yes	Yes	Yes

corresponds with the age of onset for alcohol and drug use. Also similar to alcoholism and cocaine abuse, antisocial personality disorder has been found at higher rates in AS users.

Several case reports highlight the possibility of a dependence syndrome associated with AS use. Individual users have reported feeling that their AS use became out of control. Despite a desire to quit AS use, some users have described continued use as a result of withdrawal dysphoria or fear of losing weight, strength, or muscle mass.

In DSM-5 substance use disorder, one or more of eleven different criteria may be present (1). DSM-5 substance use disorder severity is estimated by the number of criteria present. There are few studies of the presence of DSM-5 substance use disorder criteria in AS users. However, some studies using earlier overlapping criteria have been published.

Brower et al. (87) completed a survey of 49 AS users to determine the prevalence of DSM-IV TR dependence criteria for AS. Ninety-four percent of the users reported at least one dependence syndrome, with 57% reporting three or more dependence symptoms with AS use. The most prevalent dependence symptoms reported by the AS users were withdrawal symptoms, more substance taken than intended, large quantities of time spent in AS-related activities, and continued AS use despite AS problems. Users who reported dependence symptoms were more likely to have had more cycles of AS, used higher doses, felt they were still not big enough, and had aggressive symptoms.

There is limited evidence to support a family history of alcoholism or drug dependence in AS users and also not enough data to determine the prevalence of polysubstance abuse in AS users. Investigation of both these factors is necessary.

Despite the phenomenologic similarities, some important differences remain between alcohol, cocaine, and AS use. The primary reason for AS use is not for a psychoactive effect. Motivation varies for initiation and maintenance of AS use but primarily reflects the user's drive for development of strength, muscle mass, and improved physical appearance. Although users report increased self-esteem and energy, the compounds are not used primarily for a euphoric effect. This difference remains a significant challenge to the AS addiction hypothesis.

Biologic mechanisms for addiction with AS compounds have received limited research attention. Support for an animal model of anabolic steroid abuse and dependence is weak. Rats and mice demonstrate limited reinforcing behaviors when allowed to self-administer anabolic steroids (88). Hamsters studies suggest that some individuals will self-administer high doses of anabolic steroids. The hamster model suggests the reinforcing effect of androgens in animals is milder than for alcohol or cocaine. Further study of the physiologic and psychoactive effects of AS use will need to address the effects of high-dose use, withdrawal, and evidence for development of craving

The AS addiction hypothesis in humans continues to have weak support. Further epidemiologic, clinical, and basic science study will be necessary to more completely understand the psychopharmacology and psychiatric effects of these compounds.

17.3.4. Treatment

Case reports have documented substance-dependence treatment seeking in AS users, the extent of this treatment-seeking behavior appears small. Clancy and Yates (89) reported results from a national survey of substance-abuse treatment directors. Eighty-one percent of surveyed directors reported no patients with AS use presenting for treatment at their facilities over a 1-year period. Those reporting AS-using patients did note DSM-IV TR psychoactive substance dependence for AS.

Rates of treatment seeking in anabolic steroid users may increase as the wave of new users in the 1990s and 2000s begin to experience chronic use medical and psychiatric complications (90). Treatment may need to include interventions to normalize male hypothalamic-pituitary-gonadal axis function. Antidepressant treatment many address anabolic steroid related depression. There is some evidence opioid antagonists block anabolic steroid use in animals (91). The clinical implications of this finding is unclear.

17.4. Eponyms and Cultural Syndromes

Eponyms and cultural syndromes important in psychiatry are summarized in Tables 17.5 and 17.6 (91–100). Psychiatric diagnostic classification has moved away from the use of eponyms. However, they continue to be used in clinical settings and are part of the history of psychiatric description and classification.

TABLE 17.5 Psychiatric syndromes identified with eponyms.

Eponym	Description	Found in	Reference
Capgras delusion	One of the delusions of doubles. A belief that a person, usually a close family member, has been replaced by an imposter	Schizophrenia, mood disorders, psychosis and dementia	[92]
Clerambault's delusion	A delusion usually held by a woman that a famous or wealthy person is in love with her; also known by the term pure erotomania	Paranoid schizophrenia, paranoid disorder, and psychosis due to a general medical condition	[93]
Cotard's delusion	A delusion that all has been lost including money, possessions, and parts of the body such as the heart or other organs; the delusion may include the belief that the person is dead	Schizophrenia, psychosis due to a mood disorder or a general medical condition	[94]
Couvade syndrome	The experience of signs and symptoms of pregnancy or labor by the husband of a wife who is pregnant or in labor	No psychiatric disorder and possibly anxiety disorders	[95]
DaCosta's Syndrome	The syndrome, also known as neurocirculatory asthenia, characterized by easy fatiguability, chest pain, dyspnea, and palpitations	Many cases probably panic disorder	[96]
Fregoli's delusion	The reverse of Capgras delusion; strangers are identified as familiar friends or family members	Schizophrenia, psychosis Due to a mood disorder Dementia	[97]
Ganser's syndrome	A syndrome where responses to questions are approximate but not correct; also described as hysterical pseudodementia	Schizophrenia, bipolar disorder, psychosis due to a mood disorder, malingering	[98]
Kleine-Levin Syndrome	Periodic episodes of hypersomnia accompanied by bulimia	Thalamic lesions	[99]
Kluver-Bucy	The loss of facial recognition, rage reactions, hypersexuality, and memory deficits	Surgical removal of both temporal lobes	[100]
Othello's delusion	The delusion of infidelity by the spouse	Paranoid disorder, Schizophrenia, psychosis due to a mood disorder or a general medical condition Alcohol dependence	[101]

TABLE 17.6 Cultural psychiatric syndromes.

Cultural syndrome	Description	Culture	Reference
Amok	Unexpected rapid development of agitation; accompanied by obtaining a weapon and attacking everything in sight until apprehended	Malaysia	(102)
Dhat	Delusion that sperm is leaking from the body through urination, resulting in weakness	India	(103)
Koro	An acute anxiety state characterized by fear that the penis will retract into the abdomen, resulting in death	China and Malaysia	(104)
Latah	A syndrome of echopraxia, echolalia, and coprolalia; behaviors may involve putting one's self in dangerous situations	Malaysia described in Africa, Japan and Russia	(105)
Piblokto	Attacks of bizzare behavior, including screaming, running about, and tearing off clothing	Eskimo	(106)
Voodoo	A delusion of possession by devils or evil spirits.	Haiti and Africa	(107)
Windigo	A delusion of being possessed by a cannabalistic monster (windigo)	Canadian Indians	(108)

Some of more important culture-bound syndromes are summarized in Table 17.6. Culture-bound syndromes are present throughout the world. These categories have been the subject of review (108). Knowledge of these descriptive syndromes highlights the role of the culture or in the experience and description of symptoms related to stress and brain disorders.

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Part II
Child Psychiatry

18
ADHD and the Disruptive Behavior Disorders

Elena B. Metcalf, M.D.*

Abstract Although it has now been reclassified as a Neurodevelopmental Disorder, Attention Deficit/Hyperactivity Disorder (ADHD) frequently overlaps with the Disruptive, Impulse Control, and Conduct Disorders such as Oppositional Defiant Disorder (ODD) and Conduct Disorder (CD), forming a heterogeneous group of childhood onset behavioral disorders that have traditionally been lumped together as Disruptive Behavior Disorders (DBD). These frequently comorbid disorders cause significant disturbance and distress within the child's environment, usually school and/or family, as well as causing severe developmental and psychosocial dysfunction for the individual. ADHD is characterized by symptoms of inattention, impulsivity and hyperactivity, ODD by hostility, anger, argumentativeness, defiance, and CD by aggression, deceitfulness, and violation of rights of others. The DBDs play an enormous social role because they represent a high risk for developmental trajectories that harbor psychosocial, economic, psychiatric, and criminal morbidity across the lifespan and have significant socioeconomic and health impact on a national level (1). The DBDs may share comorbidities and some etiologic and pathophysiologic characteristics, however, their clinical manifestations, developmental trajectories, and biologic substrates are distinct.

The explosion of neurobiological literature about the Disruptive Behavior Disorders, most specifically on ADHD, reflects the complex, fluid, and often-contradictory manifestations of brain-behavior relationships. This complexity is enhanced further by the accumulating research demonstrating significant differences in manifestations according to age, cognitive status, gender, comorbidities, psychosocial context, and treatment response. There is an enormous degree of individual variation shaped by the transaction of biological and environmental factors, which again has major implications for prevention and diagnostic and therapeutic interventions. For practical purposes, the current discussion will focus on each condition separately.

Keywords Disruptive behavior disorders · ADHD · Comorbidity · Gender · Preschool · Children · Conduct disorder · Psychopharmacology · Prevention

18.1. Attention Deficit/Hyperactivity Disorder

18.1.1. Description

ADHD is a complex neurodevelopmental syndrome characterized by developmentally inappropriate dysregulation of attention, impulse control, and hyperactivity, which is discrepant to the developmental status and cognitive competence of the individual. Commonly seen associated symptoms are perceptual and motor coordination problems and affective dysregulation. It is the most common neurodevelopmental disorder diagnosed in children, manifesting usually in the preschool years and thought to affect up to 5.4 million children in the US (2). It is a chronic and usually lifelong condition, persists in the majority of cases into adolescence and adulthood, and is estimated to have an adult prevalence of about 4% (3). Hyperactivity and impulsivity and emotional dysregulation are the most obvious and impairing symptoms in early childhood because of their stressful effects on family,

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E.B. Metcalf, M.D. (✉)
Fellow, Department of Psychiatry, Division of Child and Adolescent Psychiatry, University of Minnesota School of Medicine, Minneapolis, MN, USA
e-mail: metca058@umn.edu

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social, and preschool functioning. As the individual matures, hyperactivity usually diminishes, but internal restlessness, impatience, impulsivity, and attentional problems, as well as distractibility and forgetfulness, persist and impede development on all functional levels. There is often a striking discrepancy between cognitive potential and emotional and behavioral immaturity, which leads to peer rejection and poor self-esteem, which are major predictors of negative social outcome. The significance of the syndrome lies in the fact that not only do the ADHD symptoms by themselves block individual self-realization, but, in the majority of cases, they are associated with comorbid disorders. Depending on personality and psychosocial factors, they can lead to lifelong maladaptations and economic, social, and emotional adversity. The economic impact associated with ADHD in adults is calculated to be between $87 and $138 billion/year through reduced productivity and salary loss alone (4).

Because of its high prevalence and because of the evidence that early diagnosis and treatment clearly diminish the adverse impacts of ADHD (5), the American Academy of Child and Adolescent Psychiatry (AACAP) has recommended that all children presenting for mental health and behavioral disorders be screened for ADHD (6). And because the vast majority of children with ADHD are treated by primary care physicians rather than psychiatrists, the American Academy of Pediatrics (AAP) has developed guidelines for diagnosis and treatment of ADHD in the primary care setting (7).

The core features of ADHD are considered to be deficits of "executive function", i.e., dysfunctions of working memory and response inhibition to inappropriate actions, thoughts, and feelings; impaired attention, planning, impulse control, mental flexibility, and activity regulation (8). These deficiencies unfold throughout the lifespan with shifting symptomatology and consequences depending on age, gender, cognitive and comorbid status, and social context. ADHD is characterized by a high rate of comorbidities with other neuropsychological disorders such as language or learning disabilities, as well as with psychiatric disorders, which results not only in more severe and complex lifetime impairment for the individual, but increases the enormous burden of ADHD for society as a whole (3, 9). Besides the obvious effects on educational, vocational, and psychosocial outcomes, ADHD is also associated with increased medical morbidity and costs in accidents, hospitalizations, substance abuse, and teen pregnancy (10). Nationally, $21–$44 billion are spent each year in incremental health care costs for children with ADHD, with an additional $15–$25 billion in excess educational costs (4). Depending on personality and psychosocial factors, only a minority of persons diagnosed with ADHD in childhood show a benign life trajectory. Despite this bleak picture, there are many individuals who have managed to achieve star status despite or perhaps even because of the vagaries associated with this condition. Leonardo DaVinci, Wolfgang Amadeus Mozart, Benjamin Franklin, Thomas Edison, Albert Einstein, Abraham Lincoln, John F. Kennedy, and champion swimmer Michael Phelps, to name just a few of a long list of iconic figures, have been described with symptoms of ADHD. Clearly the factors that shape positive as well as negative outcome need as much exploration as the syndrome itself.

Historically, a clinical picture compatible with ADHD has been described for millennia and undergone a series of labels based on etiologic and functional conceptualizations. From Hippocrates, who in 500 BC described the symptoms as the result of an imbalance of humors, to the description by Still in 1902 of a genetic "moral defect" of inhibition (11), to its reframing as a disorder of attention as the core deficit, the syndrome continues to be conceptually a moving target. This is exceptionally true for the current state of affairs, where the understanding of ADHD as an executive function disorder has been broadened to contemplate a more global disorder of neurodevelopment. It is moreover becoming increasingly evident that what we clinically call ADHD is in fact the manifestations of many different disorders of multiple underlying neurobiological pathways.

ADHD is a perfect example of the nature–nurture controversy. On the one hand, it is a validated psychiatric diagnosis (12), on the other, it continues to be controversial because its symptoms are qualitatively within the spectrum of normal human behavior and temperament and attain pathological significance only at their extremes (13). Although diagnosis continues to be based on clinical indicators of impairment, ADHD is associated with objective neuropsychological deficits, changes in brain volume, and increased slow wave electroencephalograms (14). It is controversial because as a developmental disorder it evolves transactionally from conception within a social as well as biological context, so that ADHD symptoms may both cause and be manifestations of social, medical, emotional, and other neurodevelopmental conditions. It is diagnostically further complicated by the fact that the symptoms show a great deal of intraindividual variation and inconsistency and are experienced and described more by relevant persons in the child's (or adult's) environment than subjectively experienced by the child him/herself. In other words, the objective symptoms, the subjective bias of the "eye of the beholder" (teacher, parent, spouse, etc.), and the cultural and specific context that defines abnormality and impairment must be taken into consideration.

18.1.2. ADHD Criteria in DSM-5

There has been an explosion of information about psychosocial, biologic, and neuropsychological correlates of ADHD and other neuropsychiatric disorders gained in the last 15 years. Although there is now an FDA approved brain-wave test for ADHD, it remains defined and diagnosed by behavioral manifestations rather than laboratory tests. There are some variations among diagnostic systems defining ADHD, including the World Health Organization International Classification of Diseases (ICD 10), and DAMP (Disorder of Attention, Motor control and Perception, a system used primarily in Scandinavia) (15). However, The Diagnostic and Statistical Manual of Mental Disorders (DSM) classification system (16) is the prevalent system in the US and in

international research. The DSM diagnostic criteria for ADHD represent a somewhat surgical approach to dissecting the actual clinical phenomenology of ADHD from its complex manifestations and context. The DSM-5 Criteria are based on extensive field trials of ADHD symptoms, in which two behavioral dimensions may be identified, one associated with inattention and cognitive disorganization, and the other with impulsivity and hyperactivity, occurring alone or in combination.

There are several areas of discussion associated with criteria ABCD, regarding the age of onset, the occurrence across contexts, and the exclusionary criteria (17).

Criterion A: The minimum number of symptoms necessary for diagnosing older adolescents (>17 years) and adults has been decreased from 6 to 5, reflecting typical evolution of the disorder with age and development.

Criterion B: Age of onset has been increased to 12 years, a change from the previous DSM version, which stipulated onset prior to age four. This change conveys the importance of clinical presentation in childhood, while reflecting the difficulties in establishing precise age of onset retrospectively. While children who are disruptive, impulsive, and hyperactive are usually identified in their preschool years, diagnosis of children with predominantly inattentive symptoms may be delayed because inattention and cognitive disorganization may not be noticed in the preschool and early elementary years. These symptoms often become impairing only when academic and organizational demands accelerate in the later school grades or even in adulthood.

Criterion C: Cross-situational impairment is required for diagnosis but may not be consistently observed; for instance, behavioral dysregulation, oppositionality, and aggression may be obvious at home from toddlerhood, but may be well controlled in a structured and developmentally effective preschool or daycare environment. Children with ADHD have low adaptability and are often exquisitely sensitive to the "goodness of fit" with their physical environment, teachers, parents, siblings, and peers, which may be reflected in the often highly disparate behavior ratings one finds between teachers and parents, and between teachers from one grade to the next (18, 19).

Criterion D refers to the requirement for clear evidence of functional impairment. The core impairments in ADHD are academic underachievement and poor peer relationships due to peer rejection. The presence and degree of functional impairment is clinically more relevant than the absolute number of ADHD symptoms, and has higher predictive significance for outcome (20). Gordon and colleagues (20), in an analysis of four longitudinal epidemiologic studies of ADHD, pointed out that in all four studies, the link between impairment and symptoms was weak, with DSM symptoms predicting at most 25% of the variance of impairment. Accordingly, prevalence rates were found to diminish when impairment criteria were applied. On the other hand, ADHD with significant impairment may be underdiagnosed if impairment is ignored and symptom counts do not meet threshold levels, which is frequently the case for adolescent and adult ADHD (20).

Criterion E: The exclusionary criteria have been revised to permit codiagnosis of ADHD with Autism Spectrum Disorders. Close attention must be paid to differential diagnosis given the frequent overlap of impulsivity, hyperactivity, and attentional dysregulation in other neurodevelopmental, mood, anxiety, and impulse-control disorders (21), and the frequent comorbidity of mood disorders with ADHD (9). This overlap will be discussed further in the section about comorbidities.

The DSM-5 symptom checklists are prefaced with the requirement that the behaviors interfere with functioning and development. The adequacy of the family, social, and school environment as well as age and cognitive-adaptive status of the child therefore need to be taken into consideration in order to assess how the child's ADHD symptoms are related to the environment, and if behavioral or academic expectations are appropriate for the age and development of the child. This is especially relevant when preschoolers and toddlers present with difficult behavior. Neurodevelopmental delays in toddlers and preschoolers are frequently associated with behavioral dysregulation, poor frustration tolerance, impulsivity, and avoidance behaviors and may mimic early signs of ADHD (22). On the other hand, inexperienced, stressed, emotionally dysregulated, or isolated parents may misinterpret the normal developmental agenda of increased autonomy and exploratory drive in young children as hyperactivity and ADHD (23). The parental expectations, socioemotional health, and possible observation bias of the caretakers must therefore be considered, and observations of less involved individuals included in the behavioral assessment of very young children. It is important to remember that there is an increased frequency of socioeconomic adversity and neuropsychiatric disorders in other family members of children with ADHD, which increases the risk for maladaptation and persistence of disruptive symptoms from early into later childhood and adolescence, and for the development of behavioral and emotional comorbidities (24).

18.1.2.1. Inattentive vs. Hyperactive-Impulsive Symptom Spectrum

Considerable clinical and neuropsychological differences exist between the inattentive and hyperactive presentations, indicating the heterogeneity underlying the diagnosis. Differences are found with respect to gender distribution, functional impairments, comorbidities, and pharmacologic response (25, 26). Hyperactivity is the symptom driving behavioral impairment and comorbidity with ODD, whereas attention problems drive academic impairment (27, 28). The combined type has the worst of both worlds, showing both academic impairment and ODD symptoms in about 50%, and is the most common presentation in both genders (28). The hyperactive-impulsive presentation is usually not associated with academic problems, and in fact is correlated with above average academic performance in a significant proportion (27). However, about 30% of children are behaviorally at risk because of associated ODD symptoms (27).

The predominantly inattentive form of ADHD (ADHD-I) is characterized largely by symptoms of cognitive dysfunction, underarousal, poor working memory, slow cognitive tempo, forgetfulness, and avoidance of mental effort (29). These children are usually older at diagnosis, more likely to be female, and are more likely to have comorbid internalizing rather than externalizing disorders, learning disabilities, and speech and language problems (26, 29). Children demonstrating predominantly inattentive behavior are socially impaired because of withdrawn behavior rather than impulsive intrusiveness. There is low comorbidity between inattentive ADHD and ODD symptoms. Community samples have found that a higher proportion of girls have the inattentive subtype than the other two subtypes (1:2), and in referred samples, inattention is found twice as frequently in girls than boys (30). Because inattentive children are not disruptive, problems may go unnoticed; they are underreferred, and often only identified when comorbidities or academic problems emerge.

18.1.3. Epidemiology

18.1.3.1. Prevalence

ADHD is the most commonly diagnosed neurobehavioral disorder of childhood. Prevalence rates vary from 3 to 12% in large epidemiologic studies, with 6.7–7.5% appearing to be the most consistent range. The most recent National Survey of Children's Health, conducted by the CDC in 2007, and based on telephone interviews with over 100,000 families, reported 9.5% (5.4 million) US children, age 4–17, that had ever had a diagnosis of ADHD. The rate in boys was reported to be 13.2%, versus 5.6% in girls. The rates increased with age: 6.6% in children less than 11 years; 11.2% in children 11–14 years old, and 13.6% in 15–17 year olds. There were large prevalence differences by state, with the lowest rate (5.6%) in Nevada, and the highest (15.6%) in North Carolina. There was no significant difference between white and black respondents (9.9% vs. 10.1%, respectively), however rates in multiracial children (14.2%) were higher than for other racial groups. Hispanics reported rates almost half those of non-Hispanics (5.6% vs. 10.5%) (2).

A 2007 systematic review and metaregression analysis of 102 studies from all world regions (31) found a pooled international prevalence rate of 5.29%. ADHD has been identified as a clinical diagnostic entity in all countries studied, but rates vary according to diagnostic criteria, source of information, requirement of impairment for diagnosis, and geographic origin of the study. Rates based on geographic location of the population were only significantly different between the US and Africa. The fact that ADHD rates are higher in inner cities and populations below the poverty level indicates the contribution of psychosocial adversity to syndrome development, which was already demonstrated by Rutter in the Isle of Wight studies in the 1970s (32). Epidemiologic data clearly associate socioeconomic and demographic factors with the diagnosis of ADHD, i.e., family characteristics such as less likely to live with father, more likely to be poor, school characteristics such as older teachers, and higher expectations for school performance (33).

It is important to stress that Checklist studies lead to false elevations of prevalence rates and can only be used as an estimate of deviance from the norm in a particular population. Checklist studies do not rate the prevalence of ADHD using diagnostic criteria. Instead, rating scales only establish a level of statistical deviance from the normative population. Population prevalence rates established by checklist criteria are often far higher than prevalence rates reported for more stringent diagnostic criteria (20).

18.1.3.2. Gender

Historically, most of the clinical description, epidemiology, and prevalence literature has been focused on latency age boys. ADHD in boys manifests with more disruptive and externalizing behaviors than girls, so that the rate of referral and diagnosis in boys has been much higher, possibly skewing epidemiologic as well as clinical data. Girls with ADHD are underreferred, which is strikingly illustrated by the fact that prevalence rates for ADHD in community samples show a >2:1 male:female ratio, but the ratio of boys to girls referred to clinics may be as high as 10:1 (28). This referral and treatment discrepancy is highly significant because girls with ADHD are just as much at risk for adverse long-term functional outcomes as boys with ADHD as they progress into adolescence and adulthood (34). Although for most aspects of female ADHD, it is not gender, but ADHD, that accounts for functional impairment, the clinical picture differs somewhat from that of boys with ADHD in that ADHD girls have less disruptive and externalizing behaviors and higher rates of internalizing symptoms and more cognitive impairment than boys. Both genders appear to be equally vulnerable to ADHD risk conferred by psychosocial adversity (30, 34). However, boys may be more vulnerable to involvement with deviant peers (35).

In the Massachusetts General Hospital Study of Gender Differences (36), a longitudinal study following both clinic and community cohorts, the predominant subtype for both genders in both community and referred settings was the combined subtype. However, the inattentive subtype was identified in twice as many girls as boys in the clinic population. In both community and referred subjects, boys and girls showed significant and comparable impairments in psychosocial, educational, and emotional

domains. At 5-year follow-up at an average age of about 17 years, the girls with ADHD had rates of antisocial, anxiety, mood, and substance abuse disorders comparable to boys with ADHD, and significantly higher than female controls. A nonsignificant trend to eating disorders also appeared in this population in adolescence. Girls with ADHD in this study differed from boys in one surprising aspect, namely that in adolescence they showed a higher vulnerability to substance abuse than boys with ADHD, even though they had less impairments earlier on. A longitudinal study of girls with ADHD followed from childhood to adolescence found disruptive-oppositional ADHD symptoms and peer rejection in girls to be predictive of later substance abuse and internalizing disorders (37). Girls with ADHD are at high risk for early sexual activity and unplanned pregnancy. Longitudinal studies into adulthood confirm that the persistence of ADHD symptoms and continued strong association with depression and anxiety is similar for both genders, with a higher risk for substance abuse disorders and antisocial personality disorders in men (38).

18.1.3.3. Age

18.1.3.3.1. Infants

Most studies of ADHD are limited to children in middle childhood (6–12 years). However, data are becoming available about the developmental precursors of psychopathology from infancy and toddlerhood, although the DSM classification system is poorly suited for these age groups. Neuroimaging studies suggest that structural variations may be present in infancy that are associated with later executive functioning impairment (39). Models of temperament conceptually overlap the dimensions of behavioral and affective self-regulation associated with ADHD, and the "difficult-temperament" infant may represent a bridge between infant risk and development of ADHD (40).

Auerbach (41) examined temperament differences and neurodevelopmental immaturity in male newborns at familial risk for ADHD using factors derived from the Brazelton Neonatal Behavior Assessment Scale (NBAS) (42). Newborns at risk for ADHD showed risk factors not only on indices associated with temperament, namely poor state organization (irritability, problems self-quieting), but also on measures of motor maturity and autonomic stability. At 7 months of age, a subcohort of this genetically at-risk group showed decreased interest in block play, higher activity, and increased anger reactivity. These authors assert that symptoms are subtle, possibly nonspecific, and their predictive value for later ADHD or psychopathology could be a function of the interaction with caretaking environments.

Other studies have found disorganized, insecure attachment, emotional dysregulation, and sleep problems in infancy correlated with hyperactivity, ADHD, and conduct disorders at early school age (23, 43, 44). The infant behaviors may be mediated by negative parenting and/or parental psychopathology, specifically maternal depression. Hostile parenting by mothers of sons appears to be a risk factor for later ODD and conduct disorder, whereas maternal depression is more strongly associated with ADHD (45, 46). A construct of parental–child interaction that may be a mediating factor for these effects is the presence and quality of parental, i.e., maternal responsiveness. Parental responsiveness can be operationalized and indicates the parent's sensitivity and adaptation to the child's signals, states, and needs. Maternal responsiveness may not protect against the development of ADHD, however, it does appear to protect against the codevelopment of ODD/CD (45). Maternal responsiveness is also strongly associated with language development in early childhood, which, in turn affects behavior regulation (47). In fact, distractibility in early childhood as a precursor of hyperactivity in middle childhood may be determined more by caregiving and contextual factors than biological and temperamental factors (48).

This reality was aptly summarized by Erickson, who observed: "The infant age of development is based on establishment of basic trust derived from earliest experience and is dependent on the quality of the maternal relationship" (49). And to follow with Michael Rutter: "The impression of lasting effects stems from the very high probability that a poor early upbringing will be followed by a poor later upbringing. The persistence of behavioral sequelae is largely a consequence of the persistence of the damaging experiences" (50).

18.1.3.3.2. Preschoolers

ADHD may be suspected when developmentally appropriate activity and impulsivity characteristic for toddlers and early preschoolers becomes extreme or persists beyond the toddler and early preschool period. However, in about 50% of cases considered to be at risk for ADHD, symptoms do not persist, and only 5–10% of preschoolers with concerns about inattention actually continue on to develop ADHD (51). Prevalence rates for ADHD in preschoolers are quite inconsistent, depending on methods and clinic vs. community populations. The range is from about 2% in primary care pediatrics to 5.7% in community to 59% in psychiatric referral clinics (52). There is often a significant discrepancy between parent and teacher evaluations. For example, in one Japanese study, parents reported a prevalence of 31.1% of ADHD symptoms, while teachers thought only 4.3% of these children met diagnostic criteria (53). In the Canadian nationwide survey of children 0–7 years, children's behavior was rated by their mothers at 2 and again at 7 years, with 7% of children showing persistence of hyperactivity at 7 years. The persistence was associated with male gender, maternal prenatal smoking, maternal depression, and hostile parenting (54).

At this age persistent behavioral ADHD symptoms may indicate a host of disparate problems, from medical problems, such as gastro-esophageal reflux, to environmental disruption and parenting effects, to the emotional and cognitive response to developmental frustration, to autism spectrum disorders (ASD). Disrupted sleep patterns or reduced sleep quality are associated with overactivity, anger, aggression, impulsivity, tantrums, and annoying behaviors, and these problems often resolve when the underlying sleep problem is corrected (55). Toddlers and preschoolers with language delay are often very frustrated, distractible, disruptive, emotionally dysregulated, and physically expressive. Language may improve dramatically with skilled speech-language therapy and results in equally dramatic emotional and behavioral stabilizations. In contrast, impulsive, hyperactive, inattentive, and distractible behaviors are common in preschoolers with autism spectrum disorders, but it is the lack of communicative and social intent and stereotypical behaviors that should raise concerns that one may be dealing primarily with an ASD rather than ADHD. Furthermore, cognitive deficits may underlie and mimic ADHD symptoms (22). Preschoolers usually love the individual attention and activities of testing situations as long as they are able to understand and perform the requested tasks. They may do fine behaviorally and be attentive as long as they are not requested to perform tasks that are difficult for them. However, when increased task complexity such as in imitative drawing or block activities, language testing, and other cognitive challenges results in avoidance behavior, distractibility, and inattentiveness, verbal and nonverbal cognitive deficits should be ruled out.

Preschoolers with ADHD show deficits and differences from control children in intellectual, sensory, and motor performance that go beyond the core symptoms of ADHD (22). Although similar deficits have been found in school-age children with ADHD, there is a paucity of data about developmental delays in preschoolers with ADHD. However, it is important to remember that ADHD, ASD, cognitive-adaptive, and language disorders have common interfaces at this age, and may only reveal their separate identities and diagnoses with time and with appropriate interventions.

18.1.3.3.3. Middle Childhood

By middle childhood the behavioral, cognitive, and emotional streams become more separable and diagnostically recognizable. Academic underachievement and problems with social competence and acceptance emerge as the most salient impairments. Awareness of being different begins to affect the child's self-esteem, especially as it is often the result of peer rejection or name-calling. Behavioral dysregulation persists, but dysfunctions in cognition, sensory and motor, and affective domains become more evident (17, 56).

There are many ways in which ADHD children differ from their unaffected peers. Causal connections, story comprehension, and time perception are deficient compared to controls (57, 58). Children with ADHD show restricted cognitive flexibility (59), which may manifest as stubbornness, oppositionality, or avoidance behavior. Cognitive disorganization, impaired working memory, poor reading comprehension, and procrastination emerge in middle childhood, and affect academic performance and especially homework activities (17). They have difficulty starting and completing tasks and have difficulty self-monitoring (60). They are often clumsy with complex fine motor tasks (61), and in visual-motor integration, which manifests in poor handwriting and impairment in written schoolwork. Adaptive function in daily living skills, such as maintaining personal hygiene or taking on household responsibilities, is immature relative to cognitive levels (62). Although they are inattentive and distractible with chores, homework and even on the sportsfield, they may spend hours transfixed watching television or playing computer and video games. They are emotionally and behaviorally very context dependent (57), for instance may do very well with one teacher, but may be oppositional and resistant to another. They are emotionally dysregulated, attention seeking, difficult to satisfy, tend to overreact to current and anticipated experience, and are especially intolerant of disappointment and negative experience (63).

A frequent complaint of parents is emotional and behavioral immaturity, such as silliness and inappropriateness, a preference for playmates, activities, and toys that are considerably below age and cognitive level, and a remarkable lack of insight into their own behavior, while being extremely sensitive to rejection and criticism.

However, it is very important to acknowledge that their emotions go both ways: they are also often very affectionate, enthusiastic, generous, forgiving, eager to please, very responsive to individual attention especially from other adults, and are often deeply hurt and baffled by the rejection they experience from their peers.

Academic failure due to core ADHD symptoms and associated cognitive, language, and learning disabilities, which are found in 30–50% (9), lead to poor self-esteem and acting-out behavior, conflictual family, and peer relationships and increase the risk for depression. Peer rejection may happen already to hyperactive, intrusive, impulsive preschoolers, but becomes much more evident and perceived by middle childhood, where it quickly leads to loss of self-esteem and confidence. Half of children with ADHD suffer from peer rejection, which appears to be the primary mediator for the relationship between ADHD and depression in both younger and older children with ADHD, and is a powerful predictive factor for depression in adult ADHD, particularly in women (64). Academic performance in fact may not be an issue in a bright child with ADHD, but whose impulsive and unmodulated social approach may lead to significant impairment in family and peer relationships from early childhood. Academic underachievement and peer rejection in association with ADHD convey separate but additive risk for developing of internalizing and externalizing behaviors, substance abuse disorders, and school and occupational failure in adolescence and adulthood (65).

Erik Erikson refers to middle childhood as the stage that is determined developmentally by the conflict between industry and inferiority: "the child's danger, at this stage, lies in a sense of inadequacy and inferiority. If he despairs of his tools and skills or of his status among his tool partners, he may be discouraged from the identification with them and with a section of the tool world" (49).

18.1.3.3.4. Adolescence

In the transition from childhood to adulthood, powerful changes occur in physical development, sexuality, peer and family relationships, and cognitive, moral, and emotional development. In previously emotionally healthy children, this transition is not as tempestuous as lore would have it. However, adolescence increases the risk for emergence or consolidation of previously latent, cognitive, behavioral, and emotional problems, which appears to be driven by genetic-biologic factors and shaped by family and peer relationships and academic performance. The persistence of ADHD into adolescence is also strongly associated with familial occurrence, psychosocial adversity, and preexisting psychiatric comorbidity (24, 66). Impairing symptoms continue into adolescence in 60–85% with only a small minority showing remission. Hyperactivity decreases, but inattentiveness and impulsivity persist (56). Comorbidities with anxiety disorders, depression, and dysthymia increase from the already high rate of about 30% in middle childhood to 35 and 50% respectively by mid-adolescence. Adolescent-onset mania may be suspected in depressed children with chronic irritability and explosiveness (9). Quality of life is affected in all domains: 50–70% of children with ADHD have few or no friends, the school dropout rate is estimated at 32–40%, and the college completion rate 5–10% (10, 67, 68). Adolescents with ADHD are at a twofold to fourfold risk compared with normative peers to be involved in automobile accidents (69); other risk-taking behaviors are increased, such as unprotected sex, with an increased teen pregnancy and STD rate in some studies (10). Eating disorders present a risk in girls with ADHD who are experiencing academic and peer problems, probably as a result of seeking peer acceptance and impulsive behavior (64). ADHD has also been correlated with bulimia in obese adolescents of both genders, independently of mood disorders (70).

The increased rate of psychiatric disorders in adolescence is multifactorial, driven on the one hand by familial predisposition, physical change, and environmental stressors and on the other by adolescent-specific cognitive and affective development, increased introspection, and self-appraisal (71). Sociocultural factors play a strong role in shaping the course of adolescence, so that coping mechanisms as well as issues such as school attendance and dropout rates, adolescent sexual behavior, substance use, and problems with the criminal justice system, must be considered in context, rather than solely being the results of individual pathology.

18.1.3.3.5. Adults

Although this discussion about ADHD is restricted to children, mention of adult ADHD is appropriate, since a significant portion of the parents of children with ADHD themselves have ADHD and associated comorbidities. Frequently it is the child's evaluation and treatment that leads to the parents' realization of their own disability, and frequently the first step in treating the child is addressing the parents' problems. Although adults may not meet full symptom criteria, it appears that impairing ADHD symptomatology persists into adulthood in about 65% of childhood diagnosed ADHD (4). There also is a subgroup of adults whose symptoms did not appear or result in impairment until later childhood who nevertheless meet all other diagnostic criteria and show significant impairment (72). The adult prevalence is estimated to be between 4–5% (3, 4).

The majority of adults have significant psychosocial dysfunction, including lower educational and occupational status, have fewer friends, sire more children in early adulthood, and have higher divorce rates than controls (1, 10, 72, 73). They are at substantially higher risk for antisocial personality disorders, and mood and anxiety disorders, and for behavior leading to arrest. In fact, reported prevalence of ADHD among incarcerated males may be as high as 40%, and is highly associated with learning disabilities and affective disorders (74).

18.1.4. Comorbidity

Comorbidities with at least one neurodevelopmental or psychiatric disorder occur in at least 80% of persons with ADHD, and 60% have two or more comorbidities (9). The greater the number of comorbidities, the more severely the cognitive and psychosocial functions of the individual are affected (75). Awareness of this high likelihood of comorbidity, and diagnosis and interventions has the same urgency as treatment of ADHD in order to decrease the severe psychosocial stressors that are the inevitable consequences for the child and his/her family (76). There is virtually no research literature that explicitly describes the development and course of children with "pure" ADHD, which clearly exist and could in fact represent a specific subcategory of ADHD that deserves investigation.

18.1.4.1. ADHD and Other Neurodevelopmental Disorders

Children with ADHD are different cognitively as well as affectively from children without ADHD. About 30–50% of children with ADHD have other neurodevelopmental disorders such as dyslexia and language disorders. It appears that such co-occurrences are not based on single factor linear causality, such as attentional dysfunction leading to impaired perceptual processing which then leads to reading disorders. It appears instead that they may be etiologically multifactorial, in that disparate conditions share genetic and cognitive traits that account for their co-occurrence (77). The surprisingly high rate of 25–40% comorbidity of ADHD with dyslexia is an example of such a putative genetic pleiotropy, in which one gene may exert effects on different cognitive functions.

Speech-language delay and disorders occur in 30–50% of children with ADHD (78), and frequently precede the development of reading disorders. The etiologic complexity of these comorbidities is illustrated by the fact that both language and reading development are strongly affected by environmental-caretaker factors as well as genetic factors (79). Language disorders that persist into adolescence are in and of themselves associated with higher degrees of cognitive, behavioral, and emotional disturbances (80), as is the nonverbal learning disability or right hemisphere syndrome, which is frequently associated with ADHD and is characterized by average language ability but difficulty with social cognition, and deficits in visual-integrative, mathematics, and graphomotor competence (81).

Children with Autism Spectrum Disorders have a 20–50% rate of comorbid ADHD as well as the characteristic social-communication deficits (82). Developmental coordination disorder is identified in about 50% of children with ADHD, and indicates more severe cognitive involvement as well as psychopathology. Conversely, virtually all children with movement problems are at risk for problems in attention, learning, and psychosocial adjustment (83). About 55% of children with Tourette's syndrome have comorbid ADHD (84).

Children with mental retardation have similar prevalence rates of ADHD as children with typical intelligence. However, the concurrence of ADHD increases the severity of functional cognitive impairment (82).

18.1.4.2. Psychiatric Comorbidity

18.1.4.2.1. Mood and Anxiety Disorders

Mood and anxiety disorders frequently have symptoms of inattention, impulsivity, and hyperactivity that may be misdiagnosed as ADHD. However, at least 25% of children with ADHD are thought to have comorbid anxiety and close to 50% may have mood disorders, including dysthymia and Major Depression (9). Community and psychiatric referral cohorts show the same rate of comorbidities, and in both, the prevalence of comorbidities increase markedly with age. The Massachusetts Longitudinal studies of children with ADHD found that 29% of 11 year olds with ADHD met criteria for depression, which increased to 45% by mid-adolescence, compared to 2–5% of controls. The association of Bipolar Disorder to ADHD is as yet somewhat unclear, but it is thought that early hyperactivity may actually represent a developmental precursor to mania for a significant number of children with ADHD. In the Massachusetts cohort, 11% were found to have mania at baseline, characterized by severe chronic irritability, aggression, and explosiveness, which increased to 12% after 4 years. Lifetime prevalence of ADHD in bipolar adults is estimated at 9.5%, with onset of mood symptoms an average of 4 years earlier (13.9 vs. 18 years old) than in patients with bipolar disorder alone (85). Anxiety disorders were found in 28% at baseline of 11 years, and increased to 35% in middle adolescence, compared to 5% and 9% respectively in normals. Characteristically, anxiety (generalized anxiety, separation anxiety) and depression are found concurrently in ADHD. The severity and degree of impairment is mediated by a number of comorbid conditions, family-genetic factors, and age of onset (86), i.e., the earlier the onset, the more severe the manifestations.

An interesting diagnostic dilemma exists between ADHD and Posttraumatic Stress Disorder, especially in communities that experience high levels of community or domestic violence. Clinicians must be attentive to significant overlap of ADHD symptoms with PTSD arousal symptoms (PTSD criteria E for older children or criteria D for children under 6): irritable behavior, angry outbursts, reckless behavior, hypervigilance, exaggerated startle response, concentration problems, and sleep disturbance. It is often difficult to elicit a clear history of trauma; whereas parents and schools are likely to report behavior problems. The two disorders are phenomenologically, diagnostically, and neurobiologically independent disorders, which can coexist and combine to exacerbate stress-reactivity (87).

18.1.4.2.2. Risk Factors in Psychiatric Comorbidity

As with other neurobehavioral disorders, the development of depression and anxiety in childhood and adolescence is associated with genetic, prenatal, and early infant and childhood biological and experiential factors (86, 88). It is in this context quite striking that the role of mothers in the development of behavioral disorders is well researched, whereas the presence and role of

fathers as contributing to or protective of mental disorders has received little attention until recently (89). The importance of prenatal and early childhood environmental/psychosocial contributions to childhood mental health and developmental disorders cannot be stressed enough, since prevention and early intervention are realistic goals for many of the identified risk factors (90).

Prenatal maternal stress, substance use, anxiety, and depression are associated with risk to the cognitive and affective-behavioral development in their children, mediated by alterations in the maternal HPA and, in the case of substance use, on the direct effects of teratogens on the developing brain. Postnatal environment, which includes psychosocial adversity (low income, social isolation, marital stress, absent fathers, intrafamily hostility), parental psychopathology, and caretaking behaviors are risk factors for the development of externalizing and internalizing disorders in the offspring.

However, anxiety disorders in parents have a higher specificity for development of anxiety in their children (86) than other disorders, which is mediated by overprotective, controlling, and negative parenting. Child factors that are associated with the development of anxiety are biobehavioral dysregulation in infancy, overreactivity and developmental delays in the preschool period (91), and resulting vicious cycles of anxiety, impaired peer relationships, and further developmental and academic failure. Development and persistence of depression is less specific to the particular parental psychopathology, but associated with similar prenatal and postnatal risk factors as well as with the presence of depression in the mother during later childhood (46). The cumulative effects of poor peer relationships and academic impairments represent the specific risk factors for the development of depression in ADHD (64, 86).

18.1.4.2.3. ADHD and Oppositional Defiant Disorder

ODD can be identified in about 40–60% of children with ADHD, predominantly combined type, in about 30% with the predominantly hyperactive type and is rarely reported in ADHD-Inattentive type (9). Children with ODD are disobedient toward authority figures, often easily angered, negative, vindictive, very controlling, and easily provoked by their peers. Children with depression, bipolar, and anxiety disorders may demonstrate similar symptoms. Such symptoms may occur as a reaction to stress or abuse. Despite severely oppositional behavior toward adults, behavior toward peers may be quite peaceful. Symptoms may emerge as early as in toddlerhood to preschool age and are strongly associated with maternal depression, decreased maternal responsivity, and negative parenting practices in early childhood (23, 46). In preschoolers, ODD behavior may be severe at home, often especially toward the mother and siblings, but not evident in a well-managed structured preschool environment. When ODD persists into later childhood and adolescence, a high rate of active maternal depression, helplessness and overreactivity (92–94), and paternal negativity are contributing factors (86), and oppositional behavior spills over into the school setting. Fathers of children with ODD have an increased rate of substance abuse, negative parenting, a childhood history of ADHD, and current anxiety disorder (94). ODD is associated with intense family conflict (95), that is especially virulent in adolescence and potentiates the negative effects of core ADHD behaviors (96, 97). ODD may be comorbid with Conduct Disorder as well as ADHD, but ODD does not develop into later Conduct Disorder if the latter was not already present in earlier childhood (92). Conduct disorder is clearly separable from both ADHD and ODD, and will be discussed separately.

18.1.4.2.4. ADHD-Plus

Symptoms of ADHD can be found as a specific manifestation of neurological involvement or as secondary symptoms of systemic disorders. First, identifying an underlying medical condition is imperative for appropriate etiological treatment. Secondly, if ADHD is a manifestation of or occurs comorbidly in chronic systemic or neurologic illness, pharmacologic treatment may considerably improve quality of life. ADHD symptoms, in association with cognitive and learning disorders are frequent in: posttraumatic and postinfectious encephalopathy, fetal alcohol exposure, chronic lead poisoning, cerebral palsy, prematurity, neuromuscular disorders, especially myotonic dystrophy, neurofibromatosis, fragile X, Turner, Klinefelter, and Williams Syndromes, seizure disorders, congenital brain anomalies, metabolic disorders, as well as in a host of less prevalent neurogenetic syndromes (98).

Any chronic illness, anemia, asthma, allergies, heart conditions, renal disease, metabolic dysregulation such as in diabetes or thyroid disease, chronic gastrointestinal problems, nutritional deficiencies, and other disorders causing chronic fatigue, inattentiveness, and behavioral symptoms such as restlessness may mimic ADHD and should be considered in the presence of leading physical symptoms. Chronic hypoxia, as in congenital heart disease (CHD) and Sleep Disordered Breathing, have actually been shown to be causal for ADHD (99). Studies have shown clinically significant improvement in attentional symptoms as measured by continuous performance tests following tonsillectomy (100).

Furthermore, many medications have side effects that may affect attention and cognitive processing in some children, most significantly antipsychotics, anticonvulsants, steroids, antihypertensives, bronchodilators, and antihistamines.

18.1.5. Neuropsychology

Neuropsychological theories regarding a hyperactive, impulsive, and inattentive childhood behavioral syndrome have a long-standing history dating to the latter part of the nineteenth and early part of the 20th century (12, 101). Neuropsychological dysfunction in ADHD has since been increasingly well-characterized and documented. In the 1990s, the availability of enhanced brain imaging and measurement techniques served as a catalyst to rapid advancements in the field, with much of the research over the last decades focusing on the delineation of executive functioning and inhibitory deficits in the disorder (8, 102, 103). As seen from a neuropsychological perspective, many functional processes fall under the rubric of executive functions, including set shifting, planning, inhibition, and working memory. Primarily concerned with goal-directed and problem-solving behavior, executive functions are thought to play a role in a wide range of adaptive and goal-directed behaviors, including context-specific action selection (102, 104). Problems with behavioral inhibition, conceptualized as the ability to strategically or effortfully inhibit an automatic or on-going response, have been suggested by Barkley (8) to be the primary deficit in ADHD, with inhibitory impairments leading to inadequate time for execution of other executive functions—particularly, working memory, self-regulation (e.g., of affect, motivation, and arousal), internalization of speech, and reconstitution (analysis and synthesis).

Research to date has widely supported the presence of both behavioral inhibition and executive functioning deficits in the combined subtype of the disorder (105–107). A meta-analysis by Willcutt and colleagues identified difficulties with response inhibition, vigilance, working memory, and planning to be the most robust ADHD-related impairments. Imaging studies have linked executive and inhibitory impairments to dysfunction in multiple distributed prefrontal-striatal neural networks, particularly right prefrontal cortex (especially the inferior frontal gyrus), anterior cingulate, caudate, and thalamus (108–110). However, whether response inhibition deficits—or even executive functioning or prefrontal cortex deficits more broadly—constitute the core or primary deficit in ADHD remains under considerable debate (111, 112). For instance, attention and arousal factors (e.g., variable performance and slower responding) are likely to also contribute to response inhibition deficits (113). In addition, meta-analytic studies suggest that despite findings of moderate group deficits on executive measures, many children with ADHD do not demonstrate executive impairments on any given measure. Nigg and colleagues, for instance, found that although approximately 80% of children with ADHD exhibit impairments on at least one executive functioning measure, no more than 50% of children with ADHD demonstrated impairments on any one particular executive measure and only ten percent of children had generalized/global impairments across executive functioning measures (i.e., on five or more executive functioning measures) (114). The implicit conclusion from such findings is that children with ADHD likely comprise a heterogeneous group consisting of etiologically distinct subtypes, with multiple or distinct etiological pathways that lead to similar behavioral (i.e., descriptive)-level phenotypes (as documented by the DSM-5).

The considerable neuropsychological heterogeneity among children diagnosed with ADHD has moved the field towards a search for "endophenotypes" to bridge ADHD behavioral symptoms, neuropsychological impairments, and underlying genetic or neurobiological etiologies and to explain differences in symptom clusters, comorbid diagnoses, and patterns of neuropsychological and cognitive deficits (114, 115). This approach aims to identify possible pathways to disorder—including potentially numerous genetic and environmental influences—and attempts to improve upon the DSM's behaviorally-based taxonomy by increasing specificity of the ADHD construct. This alteration in focus has produced a resurgence of interest in alternate theories of ADHD, especially those that posit neuropsychologically distinct subtypes with multiple pathways to disorder (116–118). For instance, Sergeant and colleagues' cognitive-energetic state regulation theory of ADHD (119) posits arousal (i.e., phasic alertness), activation (i.e., response readiness), and effort impairments—linked to right-lateralized noradrenergic and left-lateralized dopaminergic neural networks, respectively—to constitute the primary deficits in ADHD, with specific impairments possible in one or more of these three energetic "pools". Other prominent theories of ADHD argue the disorder to result from temporal processing deficits (120, 121), abnormalities in reinforcement-response mechanism (e.g., reward circuitry) (122), or interactions between altered reinforcement-response mechanisms and environmental factors such as social-learning, environmental conditioning, and altered appetitive or motivational systems (123) that produce "delay aversion" (124, 125).

A few additional points are relevant to current neuropsychological findings in ADHD. Patterns of impairment in the inattentive subtype of the disorder remain relatively underspecified, with the limited existing studies finding no convincing evidence for subtype differences (126). This research may, however, be confounded by the DSM taxonomy, which lumps together children without hyperactivity (many of whom are actually underactive) and those whose hyperactivity problems are "subthreshold" for the combined subtype of the disorder. This distinction is important, since some evidence suggests that children with "sluggish cognitive tempo" (e.g., inconsistent alertness and underactivity) may represent an etiologically distinct neuropsychological subtype of ADHD (127). Also as yet relatively underspecified are neuropsychological pathways towards comorbidity in ADHD. Temperamental vulnerabilities (e.g., negative emotionality), for instance, may predict development of comorbid oppositional or antisocial behavior disorders in ADHD independently of cognitive deficits (117, 118). Likewise, ADHD-related

neurocognitive impairments may predispose children towards the development of comorbid learning disabilities (128, 129). Finally, identification of the developmental trajectory of neurocognitive impairments remains in its early stages, but studies to date support the presence of impairments identifiable as early as preschool (116, 130) that persist into adulthood, despite the waning of behavioral symptoms such as hyperactivity and impulsivity (131–133).

18.1.6. Pathophysiology

The dominant hypothesis for the pathophysiology of ADHD is that of prefrontal cortical dysfunction, which is mediated by abnormalities of catecholaminergic neurotransmission in the catecholamine-rich fronto-striatal-cerebellar networks, which are the putative neural substrates for inhibitory and attentional control. The hypothesis is supported by the treatment effectiveness of stimulants, which increase the availability of extracellular catecholamines by inhibiting their reuptake from the synaptic cleft into the presynaptic terminals. Further, an increasing number of neuroimaging studies have captured structural and functional abnormalities in fronto-cortical and fronto-subcortical networks that persist in to adulthood. For example, a study of medication naïve young adults with a childhood ADHD diagnosis showed dysfunction in latero-fronto-striato-parietal regions relative to controls during sustained attention, as well as in ventromedial orbitofrontal regions during reward, suggesting dysfunctions in cognitive-attentional as well as motivational neural networks (134). The brain deficits in ADHD appear to be multisystemic, and are likely the result of differential disruptions that may occur during the development of the brain in fronto-striatal-cerebellar-parietal circuits, and may account for the inconsistency of clinical as well as of neuropsychological, morphological, and neuroimaging findings. As Casey points out, "cognitive (and neural) processes are intrinsically linked deficits in one system, and are likely to affect others in secondary ways, especially in a dynamically changing system such as the developing child with ADHD" (135).

18.1.6.1. Neuroimaging

Anatomic evidence for involvement of the frontal-striatal-cerebellar circuits is based on volumetric studies which demonstrate differences of the cerebellar vermis, caudate, putamen, and globus pallidus morphology in ADHD subjects compared to controls, as well as frontal lobe differences, with smaller volumes described of medial frontal areas including the cingulate, prefrontal, premotor, and motor cortex (136). In contrast to finding volumetric changes in discrete regions, Castellanos (137) found cerebrum and cerebellum as a whole to be smaller in all mapped regions in children and adolescents with combined type ADHD, rather than showing localized changes in fronto-striatal volumes. These differences were not affected by symptom severity, physical growth, handedness, or cognitive-comorbid parameters and remained consistent over different ages, except for a "normalization" of caudate size in adolescent probands, which was speculated to reflect the decrease in motor activity with adolescence in normal as well as hyperactivity-impulsivity in ADHD children. Significantly, morphologic changes were the same for children on stimulants as for untreated children. fMRI studies demonstrate activation differences in attention processing tasks in striatal-frontal networks (138), and in inhibitory-control tasks of cingulate, ventrolateral, and dorsolateral prefrontal cortex between ADHD and controls, but, comparable to Castellanos' findings, no differences were identified between treated and stimulant-naive ADHD subjects. (110, 139). Acute methylphenidate challenge enhances brain activity on fMRI, but this response to methylphenidate is inconsistent, not reflected in clinical test performance, and does not correspond to the fMRI activation patterns between ADHD probands and controls (138).

Affective response and mood disturbances in ADHD are thought to be correlated with volumetric differences in amygdalar regions found in children with combined ADHD and are interpreted to represent alterations in interconnectivity between amygdalar nuclei and the Prefrontal Cortex (PFC). Differences in hippocampal volume are speculated to account for differences in delay aversion and stimulus-seeking behavior (140). Further evidence for frontal involvement are EEG studies demonstrating cortical slowing (141, 142), and enhancement of Theta activity in frontal quadrants in ADHD, with males having more generalized and females having localized frontal changes (143). These EEG changes are the basis of the FDA approved Neuropsychiatric EEG-Based Assessment aid, which computes the ratio of theta and beta brain waves over a 15-minute period (144). In a blinded, prospective, multicenter study, EEG identified ADHD with 87% sensitivity and 94% specificity. Because EEG cannot identify comorbidities or alternative diagnoses, it is not recommended as a substitute for clinical evaluation (145).

It is unclear how specific neuroimaging findings are to ADHD and how much they overlap with other forms of neuropathology. It appears likely that structural-functional relationships are bidirectional, and affected by developmental and environmental factors (136). Given the clinical as well as neuropsychological heterogeneity of ADHD more definite conclusions require investigation of population samples that are defined by phenotypical homogeneity with regard to cognitive, behavioral, comorbid, and medication response characteristics.

18.1.6.2. Neuromodulators

ADHD symptoms appear to be mediated by alterations of the availability and effect of the catecholamines dopamine, and norepinephrine, which activate the circuitry and projections between the prefrontal cortex (PFC), basal ganglia, and cerebellum. Moderate levels of these catecholamines enhance, and high levels inhibit PFC function. Localization and effect of dopamine is dependent on the type of dopamine receptors that are activated, of which D-1, D-2, and D-4 receptors are the major groups. D-1-type receptors are concentrated in the PFC and their stimulation has a "U" shaped effect on PFC function, e.g., enhances working memory and attention regulation at lower levels of dopamine, but impairs it at high levels, such as with stress. Much less is known about dopamine-2-type receptor dysfunction, which appears to be associated with schizophrenia, and while there is some evidence for genotypic overlap of ADHD and schizotypy, the role of D-2 activity in ADHD remains to be clarified. D4 receptors are actually activated by norepinephrine rather than dopamine and appear to inhibit GABAergic (inhibitory) activity in PFC pyramidal cells; stimulation of D4 receptors consequently increases pyramidal cell firing. It appears that D4-receptor dysfunction, which results in increased GABA activity in the PFC with decreased pyramidal cell firing, may be associated with ADHD (146–148).

Norepinephrine receptor activity may enhance or impair PFC depending on receptor type. Activation of the postsynaptic alpha-2A receptor has enhancing effects and its agonist guanfacine improves executive functions in the PFC. Stress increases norepinephrine release at alpha-1 receptors, which has detrimental effects on PFC function. High alpha-1 activity may be associated with mania and schizophrenia, worsening with stimulants, and is blocked pharmacologically by antipsychotics (149).

18.1.7. Etiology

The many changes the concept of ADHD has undergone over time reflect different ideas about its causes. There is a point of view that considers what is called ADHD not to be a neuropathologically defined entity, but a mental construct for behavioral dysfunctional symptoms that represent a final common pathway of etiologically heterogeneous conditions. A monocausal model has given way to a transactional developmental model, in which individual factors (i.e., genetic vulnerabilities, temperament, and intelligence) interact with biologic and psychosocial factors throughout the lifespan. Recent research has returned focus on and specified the significance of the physical and social environment during gestation, infancy, and early childhood in shaping the neurodevelopmental substrate out of which mental and physical health as well as pathology, evolve (23, 90). This research gives support to the feasibility of prevention or at least mitigation of physical as well as mental disorders.

18.1.7.1. Genetics

Given the transactional conception of ADHD, the vulnerability to develop the behavioral and cognitive features associated with ADHD is highly familial. Based on epidemiologic, family, twin, adoption, and case–control studies, the heritability is considered to be between 60 and 80% (149, 150). The phenotype of ADHD is highly variable, and implies complex interactions of multiple genetic, biologic, and environmental factors. ADHD is most likely a polygenic condition, which implies the interaction of multiple alleles in the expression of ADHD, and a high if less expressive presence of such alleles in the nonafflicted population, which increases the difficulty of identifying pathogenic polymorphisms. Studies relating neuropsychological and behavioral markers to known candidate genes have led to inconsistent results (149, 150). Consequently, clinical, neuropsychological, epidemiological, and pharmacological patterns are sought as identifiers of distinct heritable subtypes that then can be researched systematically with molecular genetic methods (150, 151). Chromosomal regions containing potential ADHD predisposing loci, including 5p, 6q, 7p, 11q, 16p, and 17p, have been identified through family-based linkage studies (152). However, data associating ADHD with identifiable susceptibility genes is contradictory and still far from providing any clinically applicable consequences.

Because of the marked therapeutic effect of stimulants in ADHD, which is attributed to the inhibition of dopamine transporter (DAT) and increase of functional availability of extracellular dopamine, molecular genetic investigations have largely focused on identifying candidate genes associated with alterations of dopamine transporter and receptor (DRD) mechanisms. For example, associations were found with DAT1, DRD4, synaptosomal-associated protein of 25 kDa (SNAP25), brain serotonin transporter (5HTT), serotonin receptor 1B (HTR1B), and dopamine-beta-hydroxylase (DBH) (153). Meta-analysis examining 5 top candidate genes, all implicated in synaptic transmission and plasticity [brain-derived neurotrophic factor (BDNF), HTR1B, norepinephrine transporter gene (SLC6A2), SLC6A4, and SNAP25] found only the SNAP25 variant showing an association with ADHD. SNAP25 decreases Ca^{2+} responsiveness at glutamatergic synapses (150). A meta-analysis of 113 genetic studies by Bobb, Castellanos, and colleagues (154) supports a definite but modest role for dopamine D4 and D5 receptors, and dopamine and serotonin transporter genes in ADHD. An association of the DRD4 7- repeat allele with ADHD has been replicated

and a longitudinal study has confirmed this association in ADHD with higher cognitive function and better long-term outcome than other forms of ADHD (155).

A different approach to genetic specification suggests differentiating the phenotypes of ADHD by using dimensional as well as categorical diagnostic criteria as well as refining the subtypes as a workable path to identifying associations with susceptibility genes, for instance in differentiating susceptibility genes for different comorbidities with ADHD (156). This approach is related to the concept of "endophenotype," which has resurfaced as a way to organize and classify the mediators of genetic-phenotype relationships into operational subtypes, such as through specific neuropsychological profiles or biological markers that themselves are heritable (157). However attempts to prove that specific neuropsychological deficits play this role in children with ADHD and their unaffected family members have been unsuccessful or limited at best (115).

An example of the genotype-phenotype linkage approach is Barkley and colleagues' study of the clinical phenotypes associated with identified susceptibility genes in children with ADHD and controls enrolled in the Rochester Longitudinal Study (158). The investigation included a wide spectrum of behavioral and neuropsychological measures and identified a group of children with ADHD that demonstrated numerous behavioral main effects associated with a heterozygous DAT1 polymorphism. This group was distinguished by more severe and pervasive behavioral problems and consequences, whose effect size increased from childhood into adulthood, whereas neuropsychological tests of executive function did not associate with susceptibility genes or with distinguishing behavioral symptoms (158). Barkley makes an argument for studying the "extended phenotype" of ADHD, which he describes as the distal effect of the genotype on social relations, family, and occupational performance. Barkley conceptualizes this "extended phenotype" as being a genetically and biographically relevant endophenotype, determining the life trajectory with at least as much validity as endophenotypes identified by specific neuropsychological constellations.

In summary, the molecular genetics of ADHD supports polymorphisms in dopaminergic transporter and receptor genes, but also implies involvement of other neurotransmitter systems. Phenomenologically defined "endophenotypes" are sought as heritable mediators between genotype and phenotype to explain the heterogeneity of ADHD, but so far are only theoretical constructs. The available data does not support a unitary cause for ADHD but indicates significant polygenetic heterogeneity (159).

18.1.7.2. Physical Environmental Factors

There are many studies demonstrating the effect of early environmental adversity and influences on developmental outcome (23, 90). ADHD symptoms are frequently embedded in a spectrum of cognitive, behavioral, and physical sequelae that are strongly mediated by psychosocial and genetic variables. The following section briefly outlines the most salient environmental factors that have been etiologically associated with ADHD. Based on current knowledge, many cases of ADHD and associated neurodevelopmental disorders could be prevented or mitigated with individual as well as public health interventions.

Factors that are unequivocally associated with the etiology of ADHD are maternal smoking and alcohol use during pregnancy as well as exposure to other environmental toxins, nutritional deficiencies, prematurity, and maternal stress. However, any agent that crosses the blood-brain barrier may affect neurodevelopment. Exposure levels that have no effects in adults may have a significant impact on the developing brain. Direct behavioral effects of single agents are difficult to disentangle from the interaction with genetic, other environmental, and socio-familial factors that are frequently involved (160).

18.1.7.2.1. Prenatal Smoking

Epidemiologic and animal studies provide strong support that in-utero exposures to maternal smoking and alcohol are associated with increased risk for persistent behavioral and cognitive effects in the offspring. Smoking occurs in up to 25% of US pregnancies and increases the risk for ADHD by a factor of 2.5–3.5, when corrected for other biological and psychosocial variables (161). Most epidemiologic studies have focused on ADHD-combined type and externalizing disorders and found a strong association with prenatal smoking and nicotine exposure (162), but a careful case-control study of 100 middle-class children with ADHD-Inattentive type found an odds-ratio of 3.44 for ADHD if mothers smoked more than 10 cigarettes/day compared to mothers who did not smoke. Smoking was also associated with lower IQ scores and an increased rate of anxiety disorders in this nonreferred cohort. There was a higher prevalence of mothers with ADHD in the smoking group, demonstrating the cumulative risk of environmental and genetic factors (163).

Smoking has developmental and morphologic effects through multiple pathways, including increased CO, decreased oxygenation, cadmium accumulation, vasoconstrictive, and nicotinergic effects. The effect on the brain occurs through nicotinic effects on cholinergic neurotransmission, and on neuronal migration, replication, and differentiation early in brain development (164). Smoking alters the maternal HPA-axis and increases fetal cortisol exposure, which affects neurotransmission in cortical, hippocampal, and limbic systems, and has been shown to increase fetal ACTH, which has long-term effects on stress reactivity and behavior of the offspring (165). Increased prenatal cortisol exposure is associated with long-lasting behavioral effects that

include not only ADHD but anxiety and depression (166). Genetically mediated susceptibility to the effects of prenatal smoking has been demonstrated by the increased prevalence and severity of ADHD in children with both DAT1 and DAT4 polymorphisms who were exposed to prenatal smoking as compared to exposed children with either or no polymorphism (167).

18.1.7.2.2. Prenatal Alcohol Exposure

The teratogenetic effects on multiple organ systems of prenatal alcohol exposure, which is estimated to occur in 20–30% of pregnancies in the US, are well known (168). It is estimated that 2–5% of younger school children in the United States and Western Europe have Fetal Alcohol Spectrum Disorder (a composite of full-blown Fetal Alcohol Syndrome, Alcohol Related Neurodevelopmental Disorder, and Alcohol Related Birth Defects) (169). Alcohol affects neuronal migration, myelination, and neuronogenesis. Direct behavioral teratogenicity is demonstrated in animal studies showing specific attentional dysfunction with fetal alcohol exposure. Indirect effects are through dysregulation of the maternal HPA-axis and cortisol levels with effects on fetal brain development and function (170–172).

ADHD has been reported in 50–80% of individuals with prenatal alcohol exposure, and usually occurs within a spectrum of significant cognitive and behavioral deficits (173). The neuropsychological profile of FASD is subtly different than in ADHD without alcohol exposure in terms of executive functioning, spatial working memory, encoding, and set-shifting (174, 175). Further clarification of the neurodevelopmental differences between FASD and ADHD may have treatment implications, as stimulants are often less effective in treating attention and impulse control problems in alcohol exposed children (176).

In maternal Alcohol Use Disorder (AUD), the effects of polysubstance use, especially smoking, dose-response effects, genetic susceptibility, cognitive impairment, and nutritional and environmental factors mediate the behavioral outcomes, so that the behavioral risk conferred by the prenatal exposure alone is difficult to determine. Psychosocial confounders, particularly maternal psychopathology and male gender of the child, account for a much higher proportion of the behavioral variance than alcohol itself (168). However, even minimal amounts of prenatal alcohol exposure within an adverse social environment potentiate the behavioral risk when compared to controls. Aggressive and hyperactive behaviors are seen at 7 years of age after as little as 0.5 oz/week of fetal alcohol exposure when other factors are accounted for (168). In a "Children of Twins" study, comparing the offspring of twin pairs that were discordant for alcohol use, Knopik concludes that genetic factors (i.e., maternal ADHD, which leads to maternal AUD) act independently of alcohol exposure, and represent a cumulative risk for ADHD with alcohol exposure (177).

18.1.7.2.3. Environmental Pollutants

The neurotoxic effects of lead and mercury are well researched and include hyperactivity and attentional deficits. Exposure of the developing brain to cadmium (through prenatal and secondary smoking, industrial waste, and diet), manganese (as supplement, in soy products, and as octane enhancer in gasoline), PCBs (the latter affecting thyroid function), and agricultural and household pesticides causes neurobehavioral deficits including hyperactivity and attentional dysfunction, which have been demonstrated in epidemiologic samples as well as in animal studies. Research on the developmental effects of the thousands of other common environmental pollutants is lacking. Environmental pollutants, genetic susceptibility, nutritional deficits, and psychosocial risk factors frequently occur simultaneously and may enhance or modify their interactions, so that it is extremely difficult to determine the effect of single factors (90, 178).

18.1.7.2.4. Nutritional and Micronutrient Deficiencies

Nutritional and micronutrient deficiencies in infants, children, and women of childbearing age have a profound impact on global health and are not restricted to the developing world. Brain, behavior, and cognitive development are affected by both protein-energy malnutrition (PEM) and micronutrient deficiencies during the course of early brain development and are etiologically associated with deficits in cognitive function and ADHD (179, 180). Globally, about 25% of children have stunted growth due to malnutrition, and in the US clinical malnutrition affects about 10% of poor children (181, 182). In a longitudinal study of a Barbadian birth cohort, Galler and Ramsay reported a 60% incidence of persistent ADHD in children followed to at least age 18 years who had protein-energy malnutrition only in the first year of life, but not later, compared to a 15% incidence in controls (183). However, in the developed world, children with systemic disorders that affect feeding or absorption of nutrients, for instance cerebral palsy or celiac disease, may also suffer nutritional deficits that may cause neurodevelopmental compromise. Maintaining appropriate and adequate nutrition during periods of rapid brain growth and neuromotor development is therefore crucial in infants with nutritional deficiencies of all causes.

Iron deficiency is the most common micronutrient deficiency worldwide affecting 1.2 billion people and is most prevalent in infants, children, and women of childbearing age. It is also common in the US: 13% of 1-year-olds, 5% of 2-year-olds, and

9–11% of adolescent and young adult women are shown to have iron deficiency, of which only 2–5% had iron deficiency anemia (184). Multiple studies show attentional, memory, and learning impairment in anemic and nonanemic iron deficiency in infancy, childhood, and adolescence. Iron fulfills multiple roles in brain function, including mitochondrial electron transport, neurotransmitter synthesis, and cortical, and hippocampal development. Iron deficiency in infancy has lasting effects throughout childhood and adolescence, but correction during infancy improves cognitive and behavioral effects. Correction of iron deficiency diagnosed in school-age and older children has also been shown to normalize the cognitive-behavioral effects (185).

Long-Chain-Polyunsaturated essential fatty acids, specifically Omega-3 FAs, have been studied not only in terms of cardiac and immunologic effects but also for their role in brain development and function. Omega-3 FAs are structural elements of cell membranes, neurotransmitters and substrates of signaling molecules, and modulators in the regulation of gene expression and have played a central role in the evolution of the brain (186). Omega-3 FAs cannot be synthesized by the body and are derived entirely from the diet. Marginal or deficient Omega-3 status during pregnancy and in early infancy has been associated with increased susceptibility to bipolar disorder and depression (187). The increased risk for ADHD and schizophrenia in persons born prematurely is thought to be the result of delayed grey matter maturation associated with decreased Omega-3 fatty acid accrual (187). Abnormalities of fatty acid metabolism have been shown in subgroups of children with ADHD who demonstrated symptoms of fatty acid dysfunction, i.e., increased thirst and dry skin (188).

18.1.7.2.5. Other Dietary Factors

18.1.7.2.5.1. Obesity Risks

The well-known worldwide increase in obesity, especially relevant in pregnant women, is associated with an increase in gestational diabetes and metabolic syndrome, which is associated with increased and lasting risk for metabolic and neurologic problems in the offspring. At this time there is no evidence for a direct causal relationship between obesity during pregnancy and ADHD.

Increasing evidence, however, points to a significant association between ADHD and obesity (189). Three mechanisms underlying the association between ADHD and obesity have been proposed: (1) obesity and/or factors associated with it (such as sleep-disordered breathing and deficits in arousal/alertness) manifest as ADHD-like symptoms; (2) ADHD and obesity share common genetics and neurobiological dysfunctions, involving the dopaminergic and, possibly, other systems (e.g., brain-derived neurotropic factor, melanocortin-4-receptor); and (3) impulsivity and inattention of ADHD contribute to weight gain via dysregulated eating patterns. This association was confirmed in a recent study by Cortese et al., which found men diagnosed as children with ADHD were twice as likely to be obese in a 33-year follow-up study compared to men who were not diagnosed with the condition (190).

18.1.7.2.5.2. Food Reactivity and ADHD

Ever since Feingold published his observations in 1977 that a salicylate-free diet originally intended to treat salicylate-induced asthma also improved symptoms of hyperactivity (191), the discussion of a possible dietary role in behavioral disturbance and specifically in ADHD has been highly partisan, with objectivity becoming a victim of beliefs and biases on both sides of the issue. Recent meta-analyses reviewing 35 years of data have done little to clarify the issues (192). Diets purported to reduce symptoms associated with ADHD include sugar-restricted, additive/preservative free, allergen-free (elimination) diets, and a non-Western "healthy" diet high in fiber, folate, and omega-3 fatty acids. Controlled studies failed to confirm the effectiveness of the Feingold additive and salicylate-free diet. Nevertheless, a small subgroup of children do seem to respond adversely to additives and preservatives administered as a challenge, suggesting that combination antigen and additive-free diet may be appropriate for children with sensitivities to food antigens or allergens and to dyes (about 8% of children with ADHD) (192, 193). Atopic children with ADHD have a significantly higher response rate to elimination diets than nonatopic children. Foods most commonly implicated include dairy, wheat, egg, chocolate, nuts, and citrus fruits. Skin tests for allergic reactivity are not reliable, and behavioral improvements may lag 2 weeks after elimination of the offending food (193).

Meta-analysis of 16 studies concluded that sugar does not usually affect the behavior or cognitive performance of children, nor does aspartame or saccharine, although, as was the case with food dyes, there may be a small group of "sugar-responders" for whom aggressive or hyperactive behavior correlate with daily sugar intake. Reactive hypoglycemia is a plausible cause of transient increase in beta activity in fronto-temporal areas, associated with exacerbation of ADHD symptoms, and can be ameliorated by a low glycemic-index diet (193).

The Australian Raine study examined the relationship between dietary patterns and ADHD in a population-based cohort of live births followed until age 14. This study found an association between ADHD and higher intake of fat, sugar, and sodium (the typical "Western" diet), while diets rich in fish, fruits, vegetables, and whole grains ("healthy" diet) were not associated with ADHD diagnosis (194).

The pathophysiological mechanisms underlying behavioral food reactivity are not known. The role of diet and nutrition certainly is not settled at this point and deserves further exploration.

18.1.7.3. Prematurity

The occurrence of premature delivery is itself highly complex and multifactorial. Multiple physical and environmental factors place enormous demands on the premature brain, and even in the absence of significant neurologic or physical sequelae, many children remain small, have mild neurologic dysfunctions or dyspraxia, and "soft" morbidities that nonetheless may have significant effects on cognitive and especially psychosocial function (195). In addition, family factors, such as parental anxiety and overprotectiveness may affect cognitive and emotional development. Children born with low birth weights are at an increased risk for ADHD and other behavioral, psychiatric, and cognitive disorders. Neuronal cell death associated with multiple assaults on the immature brain, as well as reduced essential fatty acid availability, may be some of the causative factors involved. Other factors may be increased maternal stress and cortisol levels. The risk for ADHD was found to be increased by a factor of 2.46 in a meta-analysis of premature outcomes (196), and longitudinal studies found an incidence of ADHD of at least 23% of otherwise neurologically and cognitively intact very low birth weight (VLBW) children at follow-up, although even weights of less than 2,500 g already present an independent risk for ADHD (196). Psychosocial factors mediate the severity of the developmental sequelae on behavior and cognition. Lawson carefully examined focused attention at 7 months of age in neurologically intact VLBW infants and found correlations of focused (as compared to casual) attention with cognitive as well as hyperactivity measures at 5 years of age, with risk mediated by male gender, gestational age, and maternal education (197). Other longitudinal studies have shown strong relationships between VLBW, cognitive deficits, emotional dysregulation, and lower SES at 2 years (198), and internalizing problems, peer rejection, and inattention in late adolescence (199).

In summary, prematurity and low birth weight are associated with an increased risk for ADHD and behavioral-psychiatric disorders in neurologically and cognitively intact children. Risk is mediated by gender, age, and SES/maternal education. Early anticipatory guidance should start in infancy to mitigate psychiatric and behavioral morbidity.

18.1.7.4. Chronic Hypoxia

Chronic, even mild degrees of oxygen desaturation may cause cognitive and attentional dysfunction. Cyanotic Congenital Heart Disease (CHD) and Sleep Disordered Breathing are both relatively common. The evidence is robust that the hypoxia associated with both is causative for ADHD (99). Cyanotic CHD is well known to be associated with neurodevelopmental delays. Sleep disordered breathing, such as in adenoidal hyperplasia or respiratory allergies, causes significant oxygen desaturation, ADHD, and decreased IQ. Seemingly innocuous and mundane factors such as infant seating and carriers may restrict respiratory activity and should be seen as potential sources of harmful oxygen desaturation (99).

18.1.7.5. Psychosocial Factors

As already discussed, psychosocial factors play a pervasive role in the development of ADHD. The stage is set already before birth, in that maternal mental health and stress have direct and indirect physical effects on the fetus, which may last into adulthood. After birth, the responsiveness of the primary caretakers to the infant appears to be the crucial factor that shapes and gives direction to the development of attention, perception, cognition, attachment, emotionality, and beginning sense of self of the infant. This process is beautifully described by Daniel Stern (200) and continues to be validated by infant research. Maternal responsiveness may be fragile or inconsistent: depression, anxiety, ADHD, substance abuse, multiple children, and economic pressures may interfere with the intent or ability to provide the emotional and cognitive stimulation and reciprocity necessary for normal development. Attention deficit may in fact, in some cases, be a deficit of attention. Child factors that may inhibit maternal reciprocity are also significant, such as poor maternal-child temperamental "fit," child illness with increased internal distractibility due to pain or discomfort, sensory overreactivity, etc. Other family environmental factors that contribute to later comorbidities with depression and oppositional defiant behavior may be paternal psychopathology, hostile parenting, and a chaotic family environment. Boys are rated by their parents as being more intentional and in control of their disruptive behavior than girls, and are at higher risk for being the object of hostile parenting and harsh discipline, which may be a factor leading to increased oppositionality in boys already present by preschool age (201). Low SES and family stressors are high risk factors for development of antisocial behavior in hyperactive boys, and predictive of negative adolescent peer group affiliation (gangs) already by kindergarten age (202).

The Fragile Families and Child Wellbeing Study, a multicenter study of almost 3,000 children followed from birth to 3 years, examined the cumulative effect of maternal mental health, substance use, and domestic violence at 1 year after the child's birth on child behavior at 3 years as measured by the Child Behavior Checklist (CBCL) (203). 50% of mothers had at least one adversity factor. Prevalence of child aggression, anxiety, and attention problems were between 18 and 20% in children whose mothers were depressed, anxious, or abused and increased highly significantly with cumulative maternal problems, with anxiety showing the greatest increase. Prevalence rates for all problems were much higher in families below the poverty line and lower SES

than higher SES. However, the effect of increased maternal problems on the children was the same across SES groups (203). This study demonstrates the high correlation with and cumulative effect of maternal and child problems. Unfortunately, there is no information about the factors that were associated with positive child outcomes (about 75%) in this study.

18.1.7.6. Electronic Media

TV viewing during infancy and toddlerhood has been shown in several studies to be associated with significantly increased risk for ADHD by school age (204, 205). TV watching in infants, whose brains are undergoing rapid synaptogenesis, and have high plasticity relative to experience and stimulation, may interfere with normal perceptual and cognitive development, especially in the presence of perceptual or cognitive vulnerabilities. It is also known that adult TV watching decreases the attention given to the child. This may play a significant role in environmental and social deprivation for children whose mothers are depressed and isolated (206). In older children, an association between time spent playing video games, school performance, and symptoms of ADHD inattentive type has been found (207). Swing and colleagues (208) used a longitudinal design to show that the amount of time spent watching TV or playing video games was positively related to greater attention problems. This was true even when earlier attention problems and gender were statistically controlled, ruling out the possibility that the association between screen media use and attention problems is merely the result of children with attention problems being especially attracted to screen media. Screen time was associated with attention problems in both middle childhood and late adolescent/early adult samples (208).

18.1.8. Evaluation

Since the majority of children with ADHD are treated by their primary care physicians, the American Academy of Pediatrics has issued guidelines for evaluation and management of ADHD which are virtually congruent with the preliminary guidelines by the American Academy of Child and Adolescent Psychiatry (6, 7).

Screening for ADHD should be a part of any child's mental health assessment. Any child presenting with symptoms of impulsivity, hyperactivity, and attentional dysfunction should have a thorough evaluation for ADHD. Assessment needs to be based on DSM-criteria and includes information from parents or caregivers, classroom teacher, or other school professionals, regarding the core symptoms of ADHD in various settings, the age of onset, duration of symptoms, and degree of functional impairment. Since ADHD increases and becomes more virulent with psychosocial adversity and comorbidities, information about preceding and ongoing social/familial stressors and family and emotional functioning should be obtained.

18.1.8.1. The Diagnostic Interview

The diagnostic interview with the parents as well as interview with the child, and, if possible, observation in a challenging situation, are central to the evaluation. The parents and child should be interviewed separately in order to allow free expression of concerns, avoid further injury to self-esteem, and divulge confidential information from both. A thorough medical history including prenatal and perinatal and family history is important for the consideration of etiologic factors, rule out medical conditions, and to assess risk for specific comorbidities. Developmental, educational, and daycare information, as well as social history, provide essential contextual information.

The interview with the verbal child/adolescent may lead to sometimes unexpected insight into the child's emotional state, and perception of self, peer, and family relationships and should serve to rule out significant social, thought, or emotional problems.

The physical and neurological examination should be made with respect to ruling out associated or underlying medical conditions, which are, in effect, infrequent. However, in about 50% of children with ADHD one finds indication of mild neurological dysfunction, such as abnormal neurologic soft signs, decreased muscle tone, motor planning problems, and sensory differences, which may significantly affect fine and gross motor activities. These findings are important for treatment planning. Laboratory evaluations are not useful unless clinically indicated.

A short developmental screening session with preschoolers often is a window into behavioral, cognitive, and emotional vulnerabilities. Avoidance, inattention, distractibility, or oppositionality on developmental testing are often signs of developmental incompetence rather than of a primary attention deficit.

18.1.8.2. Behavior Rating Scales

The diagnostic interviews should be augmented with information from school, teachers, and other caregivers and should include standardized ADHD specific rating scales from parents and teachers (ADHD IV, SNAP-IV-R, Vanderbilt ADHD Rating Scales, AcTers, Conners' Rating Scales-Revised), and broadband behavior rating scales that screen for associated behavioral-emotional

dysfunction in the home and school environment (BASC, CBCL Parent, caregiver-teacher report forms). Adolescent self-reports are available for the major screening systems (209). Several of these scales are free and in the public domain and can be downloaded (209). Children with ADHD usually have better behavioral control in structured situations, so that there may be significant differences between classroom, playground, and home behavior. Discrepancies between teacher and parent behavior ratings are common and do not necessarily challenge the diagnosis, but show that different aspects of the underlying condition manifest in different environments. Emotional-behavioral issues may be more pronounced at home, whereas inattention/distractibility is more evident in school. Children with ADHD may be likened to the proverbial "canaries in the coal mine" and quickly display problems with environmental "fit". Children with LD without ADHD usually are not disruptive or inattentive outside of the challenging situations.

Behavior rating scales are important adjuncts in the evaluation process for ADHD but should not be used as the basis for making the diagnosis. It should also be remembered that they reflect subjective evaluations of the child and may be colored by the emotional state, expectations, and experience of the evaluator.

18.1.8.3. Developmental/Psychological Assessments

Since ADHD is defined as a significant discrepancy of attention, impulsivity, and activity relative to developmental age, screening and if indicated evaluation of cognitive-adaptive status, communication-language, visual-motor integration, social-adaptive, as well as hearing and vision should be performed in the child suspected of having ADHD.

A formal psychoeducational evaluation assessing intelligence, memory, executive function, visual-motor integration, and achievement with standard methods may be necessary in the academically or behaviorally underperforming school-age child to rule out learning discrepancies relative to cognitive potential, which may also include giftedness. A psychoeducational evaluation can be performed free of charge by the school system for any child in a given district, provided that there is an indication. Specific speech-language and occupational therapy evaluations may be indicated to rule out a language disorder, which co-occurs in approximately 25% of children with ADHD.

In older students and adults, evaluations become more problematical because of the need to have childhood behavior information (possibly from the patient's parent or sibling) as well as current behavioral descriptors, such as from the spouse or employer.

The evaluation should explicitly identify vulnerabilities and impairments, i.e., academic, social, emotional, behavioral, and comorbidities. However, in addition to impairments, it is important to identify strengths, competencies, talents, and other self-esteem and resilience building factors that may be integrated into the comprehensive treatment plan.

18.1.9. Treatment

ADHD is a chronic disorder, therefore quality of life considerations of the child within his or her family, school, and peer context should be at the center of treatment planning. Similarly to other chronic conditions, a holistic approach needs to include lifestyle as well as medication management. Short-term and long-term treatment goals need to be specified relative to specific target symptoms, and academic and social goals need to be balanced. Educating the child and the family, engaging them as partners, and addressing both child and family generated problems is the first step. It is important to remember that at least 25% of children with ADHD also have a parent with ADHD, and that other mental disorders are increased in these families. Quite frequently, the diagnosis of the child leads to the parent's recognition of their own impairment and seeking treatment for themselves. Comorbidities need to be treated with the same urgency as ADHD, with stabilization of any acute conditions such as manic episodes, given priority.

The treatment plan should consider medication and/ or behavioral therapy as appropriate. Target outcomes should be defined and if not achieved within a given period of time, the diagnosis, comorbidities, compliance, and treatment appropriateness should be re-evaluated. A systematic follow-up needs to be pursued, and target outcomes and adverse effects should be monitored with information gathered from teachers, parents, and the patient.

18.1.9.1. Behavioral and Educational Treatments

Medication management is at the center of ADHD treatment, but supportive interventions should be considered in any child at risk for or with manifestations of ADHD. Intensive behavior management interventions within the school and home setting are shown to be sufficient in decreasing core symptoms in milder cases of ADHD, and should be considered in such cases before pharmacological treatment is begun. Consistent behavior management decreases dosage requirements when medication proves necessary (210), although short-term treatment does not appear to offer any benefit beyond that obtained by optimal medication management (211).

Behavioral treatments are especially relevant in preschool ADHD, where skilled early behavioral intervention may redirect an otherwise high-risk developmental trajectory and medication treatment may not be desired, effective, or associated with unacceptable side effects (212). Behavior management in older children does not change the core symptoms of ADHD, but it changes parenting style and effectiveness. Parenting-family training can give parents the skills to be active and authoritative agents in their children's development and behavior and to avoid the combination of helpless defeatism, hostile parenting, and chaotic overreactivity that gives rise to and maintains externalizing behavior (213, 214).

Parent training and /or developmental preschools may be available through the State Early Intervention or school systems and should be vigorously sought at the earliest possible moment. Providers who deal with young children need to be knowledgeable about state and community resources. Early Head Start, a good daycare, or preschool may provide an emotionally neutral environment, which may relieve stress for the child as well as the family and improve family interactions.

Educational interventions: School children with ADHD without learning disabilities are eligible for individualized accommodations under section 504 of the 1973 Rehabilitation Act which is a civil rights law that prohibits discrimination against individuals with disabilities and emphasizes regular class placement with behavioral and pedagogic modifications. It is unfunded but federally mandated. Children with ADHD and comorbid learning disabilities are eligible for special education and an Individualized Education Plan (IEP) under the federally funded Individuals with Disabilities Education Act, which is mandated to provide more extensive services to children with disorders of learning and encompasses modification under section 504.

Tutoring may be extremely helpful in children with specific LD and ADHD. Being able to read at grade level by third grade is associated with increased resilience in light of other developmental risk factors. ADHD behavior that is highly associated with a learning disability may resolve if the LD is successfully addressed. Social skills interventions for ADHD may be provided within the school setting but usually are obtained privately. Social skills and behavior management training in the context of ADHD summer camps improve core ADHD symptoms as well as social coping and insight and are available in some communities as academic laboratory settings. It is quite obvious that behavior management interventions require more financial and personal cost than medication management. Health insurance frequently does not pay for the intensive parenting counseling that is initially required, and parents must be willing to develop the skills, change their own behavior, and adopt a long-term perspective for success. Behavior management is similar to medication management in that it is effective only as long as it is utilized, i.e., it has no curative potential, but it does, however, teach self-control, social skills, and coping strategies (215).

18.1.9.2. Pharmacologic Treatment

18.1.9.2.1. Stimulants

In 1937 Bradley reported that amphetamine dramatically improved behavior, emotionality, and academic performance in institutionalized children with normal cognition but severely disruptive behavior (216). Amphetamines (AMP) were not routinely used in ADHD until the less potent stimulant methylphenidate (Ritalin) became available in the 1960s. Since then methylphenidate (MPH) has become the most frequently utilized and studied psychotropic agent in children, and stimulants have become the gold standard for treatment effectiveness in ADHD (217). Stimulants are by far the most popular medications for ADHD because of their large margin of safety, effectiveness, short half-lives with easily observed treatment response, and ease of administration. Side effects are low, and there is little attenuation over time.

Improvement of prefrontal cognitive tasks in "normal" as well as ADHD subjects with low doses of methylphenidate is the basis for improvement of clinical symptoms. Stimulants affect norepinephrine and dopamine release predominantly in the prefrontal cortex and fronto-striatal circuits by inhibiting the reuptake, and enhancing the release of these catecholamines at the synaptic cleft, as well as by blocking the dopamine transporter and enhancing extracellular dopamine (147).

Given the neuropathological heterogeneity of ADHD, the effectiveness of stimulants on the core symptoms in the majority of cases is surprisingly simple. Stimulants improve cognitive and academic performance as well as the core symptoms of impulsivity, hyperactivity, and attentional dysregulation. Stimulants are effective in improving ODD and CD symptoms even in the absence of ADHD symptoms (147). Stimulants are effective in all ages starting with preschoolers (218). The effects are similar in children and adults with and without ADHD and are therefore neither diagnostic nor specific. Treatment has been shown to have major effects on quality of life: Stimulant treatment is associated with less grade retention, lower school dropout rates, less absenteeism, lower rates of substance abuse, and improved reading scores (5). Hundreds of randomized short-term trials have shown stimulants to be effective in 50–75% of children with ADHD with relatively few side effects. However, the application of the outcomes of clinical research trials vs. the outcome in community settings is problematic, because clinical research trials have a strong sample bias compared to community conditions, excluding many factors that confound community treatment such as comorbid conditions and poor compliance. The distinction between *efficacy*, as used in controlled clinical research trials, vs. *effectiveness* of a treatment, i.e., the treatment response under usual clinical conditions, should therefore be kept in mind. Quality of life measures should also be considered when assessing treatment response (219).

Compared to the abundance of short-term randomized trials of stimulants, mostly of methylphenidate, comparatively few long-term studies have been completed. The benchmark of long-term clinical trials has been the Multimodal Treatments Study of Children with ADHD (MTA) (220), a multicenter randomized prospective study which compared community (including pharmacological) treatment, intensive pharmacological (mostly methylphenidate), and behavioral treatments alone and in combination with pharmacological treatment, over the course of 14 months in 579 children. The study found that compared to behavioral and community treatments, pharmacological treatment alone was superior to all other conditions in treating core ADHD symptoms. However, combination treatment was more effective than pharmacologic treatment alone in improving associated oppositional/aggressive and internalizing symptoms, especially comorbid anxiety, teacher-rated social skills, parent-child relations, and reading achievement (220). While there has been an explosion of research in neurodevelopmental disorders, mostly in the realm of genetics and neuroimaging, this study remains the foundation of clinical practice.

The community counterpart to the MTA has been the medication arm of the Rochester Epidemiology Project (5, 11). The long-term safety and effectiveness of stimulant treatment in a community setting was investigated in 283 children with research identified ADHD, whose treatment data were available from a median age of 9 years, with a median duration of 33 months and range from school entry until high school graduation. Seventy-three percent showed a favorable response rate to stimulants. About 22% of children had side effects with a higher rate of side effects for dextroamphetamine than MPH (5).

Treatment effects have been studied predominantly in latency age boys, but similar effectiveness in girls, adolescents, and adults has been demonstrated (5, 220). Effects are also similar across subtypes in most studies, with some showing greater responsiveness of the inattentive subtype to lower doses. However, outcomes are not always consistent: other studies show improved hyperactivity and impulsivity with less response of attention problems. The Preschool ADHD Treatments Study (PATS), a combination of blinded randomized and open label study of 1 year's duration in children, age 3–5 years, demonstrated that stimulants are also efficacious in preschoolers, who tended to require lower doses and had an increased incidence of side effects (218).

18.1.9.2.1.1. Stimulant Forms

Methylphenidate, its D-isomer (dexmethylphenidate, Focalin), mixed amphetamine salts (MAS-Adderall) and D-Amphetamine are the most frequently used stimulants and are available in short acting (4 hour), intermediate (8 hour), and sustained release (12 hour) forms. Amphetamines are about twice as potent as methylphenidate. The effect size of stimulants, i.e., the difference between drug and placebo effects, is 0.8–1 and provides a comparison measure between different medications for ADHD. Dosage and frequency requirements are highly individualistic and depend only in part on the size and weight of the child. It is therefore recommended to start low and titrate upward depending on treatment goals. Dosage for MPH preparations range from 0.3 to 2 mg/kg/day, with half of that for Focalin (D-isomer of MPH) and amphetamine preparations (221).

When beginning stimulant treatment, it is important to consider the target symptoms, i.e., under what conditions does the child need medication and for how long (school, homework, sports, etc.)? Timing is important also in observing the child for effects and side effects at peak level as well as possible withdrawal/rebound symptoms at trough, and allows for adjustment of medication to daily routines, meals, and bedtimes.

Short-acting MPH/MAS/D-amphetamine onset is after about 30 minutes and duration of effect is about 3–5 hours. Short-acting methylphenidate is now available in liquid form for children who have difficulty swallowing pills. Intermediate preparations (Metadate CD, Ritalin LA) onset is after about 1 hour and duration about 8 hours. Sustained release preparations (OROS-Methylphenidate/Adderall XR MAS/lisdexamphetamine) have an onset of about 1 hour, with a duration effect of up to 12 hours. Intermediate and long-acting preparations vary with respect to the immediate release component, which is 50% and 25% respectively, and may need an initial low-dose short-acting "booster". The type of delivery system, whether beaded in capsules, in a wax matrix or osmotic release form, affect absorption and availability. Once per day sustained release dosing is desirable because it improves compliance, is less conspicuous, has less abuse potential, and the effect is smoother with less "roller coaster" response from changes in levels (222–224).

A MPH dermal patch (multipolymeric adhesive system, Daytrana), releasing 10–30 mg of MPH over a 9 hour period, is approved for children 6–12 years and can be practical in children who are not able to take oral medications. It has been found safe and effective in short-term studies (225). There are anecdotal reports of local and systemic sensitization, however, which is a risk with all topical medications. Heat sensitivity of the patch needs to be considered.

Dosage requirements of stimulants vary with the individual as well as with the context. Children with prenatal substance exposures often require higher stimulant doses and are more difficult to manage medically. Behavioral interventions modify medication effects. Pelham has observed that stimulant effectiveness plateaus at lower doses under conditions of consistent behavior management and a structured environment, whereas higher doses are more likely to be required in less optimal circumstances (210).

Maintenance of a structured, daytime routine with adequate nutrition and sleep, as well as physical exercise, (which in some studies has shown to improve executive function), provides the physical requirements to optimize medication effects.

18.1.9.2.1.2. Stimulants in Comorbid Conditions

Stimulants are effective for ADHD symptoms in multiple comorbid conditions including sequelae of brain injury and other static encephalopathies; in ADHD symptoms associated with Autism Spectrum Disorders; and in mental retardation with ADHD. Careful stimulant treatment may be very effective and is not contraindicated in well-controlled seizure disorders with comorbid ADHD (226). In ADHD with comorbid tic disorders, stimulants are not a contraindication when carefully monitored (227), but should be discontinued if tics worsen or do not stabilize with alpha-adrenergic agonists (clonidine, guanfacine) (228), which have shown effectiveness in tic disorders.

Stimulants may not be as effective in treating core symptoms of ADHD when there are significant comorbidities with anxiety or mood disorders. Under these conditions, single or combination treatments with atomoxetine have been shown to be effective in some patients (229). Alternatively, SSRIs, buproprion, or tricyclic antidepressants may be helpful. The tricyclics have significant alpha-adrenergic effects but require very close monitoring because of cardiac toxicity. Stimulants should not be used in severe anxiety disorders. There is some indication that stimulants may precipitate manic episodes in previously not identified bipolar disorder, but may be used in ADHD/bipolar co-occurrence after mood stabilization (230).

18.1.9.2.1.3. Stimulant Side Effects

Stimulants have a high margin of safety. Most side effects are a result of CNS-action of stimulants and therefore behavioral or emotional. However, stomach and headache are frequent, usually mild, and of short duration. Absorption is affected by calcium and citric acid, but not by other foods, so that stomach aches can be ameliorated when stimulants are taken with a meal. Appetite suppression is frequent and chronic, but can be compensated with a good breakfast, dinner, and bedtime snack. Children should have a snack when levels are declining after short or intermediate dosages in order to prevent the convergence of hunger and rebound/withdrawal symptoms. Sleep problems are often associated with ADHD, but stimulants may also interfere with sleep if given too late in the day. Sleep hygiene, melatonin or clonidine, and a carbohydrate- rich bedtime snack may help with sleep onset. Lack of adequate and restful sleep may worsen ADHD symptoms and emotional reactivity.

Stimulants are activating and therefore may increase anxiety. Rarely stimulants may precipitate a psychotic reaction (231). Social withdrawal, emotional and activity constriction, and obsessive-compulsive behavior may be a sign of overmedication and should lead to dosage adjustment. In some children, increasing hyperactivity may be a sign of overmedication rather than undermedication. "Roller coaster" and withdrawal effects are seen more often on short-acting than intermediate or long-acting stimulants. They are usually of short duration and consist of whininess, sadness, and irritability. A nutritious snack and "quiet time" or physical activity usually can bridge this period. However, some children may withdraw or rebound with significant aggression, which may necessitate a stimulant switch or alternate medication or augmentation with an alpha-adrenergic agonist (clonidine, guanfacine). It is important to observe behavioral changes with regard to expected peak or declining levels.

Transient tics may occur as a result of stimulant treatment and usually resolve after change in dosage, discontinuation, or change to alternative drugs (228). Contrary to public opinion, stimulants do not promote substance abuse and in fact, show a protective effect to nonalcohol substance use when compared to persons with ADHD who have not been treated (232).

Occasionally stimulants cause increased diuresis and enuresis due to a minor diuretic effect. Priapism can occur. Bone-marrow suppression and leukopenia occur very rarely. There are no established recommendations regarding monitoring of CBC.

18.1.9.2.1.3.1. Cardiac Effects

Stimulants do have cardiovascular effects, and may decrease heart rate and increase diastolic and systolic blood pressure at standard therapeutic doses (233). Although cases of sudden cardiac death have been reported, increased risk is not supported by clinical data (234): sudden death on Adderall is calculated as 0.5:100,000 patient years as compared to 1.3–8.5:100,000 patient years in the general pediatric population. Sudden death in children is most often caused by fatal arrhythmias due to congenital heart diseases, such as long QT syndrome and hypertrophic cardiomyopathy. Five of the 12 reported cases of sudden cardiac death while taking stimulants had unrecognized underlying structural heart disease. While screening for a family history of sudden cardiac death is prudent, the American Academy of Pediatrics and American Academy of Child and Adolescent Psychiatry no longer recommend the routine use of EKG before beginning stimulant therapy (235). The combination of the cardiotropic alpha-adrenergic drugs and stimulants should be carefully monitored for hypotension and arrhythmias or bradycardia.

Tricyclic antidepressants and MAO inhibitors should not be given with MPH because the latter increases TCA levels, increasing the risk of cardiotoxicity or hypertension. Stimulants are contraindicated in significant arrhythmias, hypertension, liver disease, severe anxiety, and drug-seeking behavior (234).

18.1.9.2.1.3.2. Stimulants and Growth

The effect of stimulants on growth has been a topic of controversy for some time. Although the Preschool ADHD Treatment Study, which monitored children over 12 months of stimulant treatment, found that linear growth decelerated by 20% of

expected growth in 1 year, with a moderate effect on weight (236), studies in older children show insignificant decreases in growth velocity and weight gain on MPH and MAS as well as on long-acting stimulants in school-age children (237). No information is currently available on the long-term growth trajectories of children started on stimulants as preschoolers; stimulant use in preschoolers needs precise justification. Depending on symptom severity, continuous year-round dosage may be warranted, but in cases of growth plateau, drug holidays can provide crucial opportunities for catch up growth. Although growth suppression is independent of weight loss, in very young children, careful management of dosing times to provide for adequate mealtimes is important to allow adequate nutrition.

18.1.9.2.2. Nonstimulant Medications

Fifty to seventy percent of children respond to stimulants, but alternate medications and nonpharmacological and supportive interventions are necessary for the other 30–50% who do not.

18.1.9.2.2.1. Atomoxetine

Atomoxetine (Strattera) is a norepinephrine reuptake inhibitor. Its benefits include no abuse potential, no motor or tic activation, and it does not interfere with sleep. However its effect size is significantly less than that of stimulants at 0.6–0.72. Full effect is reached after 4–6 weeks (and possibly longer) of therapy. Dose is 0.5 mg/kg/day in one or two divided doses, effects last for 24 hours, which is very useful for children who have significant attentional problems in the morning. Atomoxetine may be more effective in treating core symptoms of ADHD in stimulant naive children rather than in those previously on stimulants. It may be used in conjunction with a stimulant when longer duration without sleep deprivation is needed. Atomoxetine is showing some advantage in children with ADHD and comorbid anxiety or depression; however, comedication with a stimulant may be necessary to improve core symptoms. Side effects are appetite suppression, GI upset, somnolence, occasional irritability, and aggression. Cardiac side effects, i.e., increased blood pressure and tachycardia have been reported. Suicidal ideations have been reported in 5/1357 children on atomoxetine, leading to a Federal Drug Administration black box warning (238).

18.1.9.2.2.2. Modafinil

Modafinil (Provigil) (221), originally indicated for narcolepsy, is not FDA approved for treatment of ADHD. Its mechanism of action is thought to be through diffuse cortical activation via adrenergic systems as well as through thalamic and reticular activation system attenuation. It also has a low abuse potential. It has an effect size of 0.7 after titration to a full dose after 7–9 days to an average dose of 300–400 mg/day. Side effects are headache, appetite suppression, nervousness, and sleep disturbance.

18.1.9.2.2.3. Alpha-2 Adrenergic Agonists

The antihypertensive drugs clonidine and guanfacine (221) inhibit catecholamine release, affect basal adrenergic tone, and improve prefrontal cortex function. They may be used alone or in conjunction with stimulants and are effective in impulsivity, hyperactivity, aggression, especially in young children, and in treating ADHD associated sleep disorders (239). Guanfacine is effective in tic disorders with ADHD, alone or in combination with stimulants (228). Behavioral effectiveness may not be observable for 4–6 weeks. Side effects of sedation and irritability may be significant initially, more so with clonidine than guanfacine. The potential for hypotension and bradycardia require EKG and blood pressure monitoring. Both medications are available in long-acting formulations (marketed as Intuniv and Kapvay) for once-daily dosing.

18.1.9.2.2.4. Antidepressants

The tricyclic antidepressants desipramine and nortriptyline have excellent effectiveness in improving the core symptoms of ADHD, and ADHD with comorbid tic disorders due to their noradrenergic effects (148). However, they have a narrow margin of safety because of their significant accumulation in cardiac as well as brain tissue, with a significant risk of cardiotoxicity resulting in conduction abnormalities, increased heart rate, and increased blood pressure. Effects are observed after about 4 weeks, dosages must be carefully titrated, and blood levels and cardiac response monitored with frequent EKGs. TCAs have significant anticholinergic side effects, often cause weight gain and gastrointestinal problems. Their use for ADHD has decreased sharply after reports of sudden cardiac death in several children (240).

Bupropion is an antidepressant with noradrenergic and dopaminergic neurotransmission effects. Several double-blind controlled studies have showed some efficacy in treating children and adolescents for ADHD, though results were less robust than those typically seen with stimulants (241–245). Caution should be used in those at risk for seizures.

18.1.9.3. Nonpharmacologic Treatments of Core ADHD Symptoms

Nonpharmacological treatments may need to be considered when medication response is associated with significant side effects, lack of improvement, or when pharmacologic treatment is undesirable for other reasons. Nonpharmacological treatments that have been subjected to accepted research trials are biofeedback paradigms and dietary interventions in selected populations. These interventions may be effective by themselves or within a multimodal treatment context. Many alternative and complementary treatments of ADHD that reflect cultural as well as scientific approaches are in use and cannot be discussed here. Given the fact that there are many pathways that lead to ADHD, heterogeneity of effective interventions is conceivable. A critical but open mind should be maintained toward novel approaches.

18.1.9.3.1. Biofeedback Modalities

Neurofeedback is a method of self-regulation that has been widely clinically utilized in combination with or as an "alternative" to pharmacologic treatment, especially in Australia and Europe. Neurofeedback is based on the pathophysiological model of cortical hypoarousal, which is demonstrated in neuroimaging modalities and may also be observed in quantitative EEG studies by the relative dominance of slow (theta) waves over alpha and beta waves in the frontal and prefrontal cortex in the majority of patients with ADHD (142, 143). Suppression of slow and increased production of faster brain-wave activity is achieved by operant conditioning using differing EEG feedback protocols that are determined by ADHD subtype. Thirty to fifty sessions are usually required. The results of several controlled group studies indicate that EEG biofeedback may be effective in treating the core behavioral symptoms as well as successful on the continuance performance test (CPT), cognitive, emotional, and academic performance in ADHD, either alone or in conjunction with stimulants. Improvements in these parameters has allowed reduction of stimulant doses and has persisted up to 1 year after conclusion of the NF treatment and after complete discontinuation of stimulant treatment (246). Randomized double-blind placebo controlled studies have shown similar results on behavioral and neuropsychologic parameters as well as activation of cortical areas known to be underactive in ADHD. Strehl and colleagues reported a controlled study of EEG-biofeedback in self-regulation of Slow Cortical Potentials with persistent improvement in ADHD core symptoms as well as neuropsychological parameters (247). However, methodological questions remain whether the actual agents of change are the biofeedback paradigm or contextual factors (142).

Significant improvement of hyperactivity with Actigraph-biofeedback has also been reported (248). The interactive metronome (249), a biofeedback paradigm based on synchronization of hand and foot movements with auditory stimuli, originally used in enhancing performance in sports, and widely used in movement disorders, has been shown to improve attentional and academic performance in one double-blind placebo controlled study (249).

18.1.9.3.2. Elimination Diets and Dietary Supplements

Based on the research of the last 35 years, it is difficult to dismiss summarily the findings that some children with ADHD respond favorably to individualized elimination diets (192). Behavioral improvement is more likely with appropriate elimination diets in individuals with atopic histories, family history of migraine, and a family history of food reactivity (192); younger children also seem to be more responsive. Specific target behaviors may include sleep and mood disturbances in addition to typical ADHD symptoms. Proven or suspected antigens as well as food colorings and preservatives should be eliminated for at least 3 months with monitoring of target behaviors. Challenges should then be tried for the individual suspected foods. A partial blinding may be carried out by not informing teachers or therapists. Nutritional counseling and referral to support groups is often advisable. The family must understand that dietary management requires a great deal of commitment on a long-term basis. Dietary management should be under the direction of a knowledgeable physician.

Children with ADHD have been found to have low levels of long-chain polyunsaturated fatty acids in their plasma and red blood cells, compared with controls (192). The double-blind placebo controlled Oxford-Durham study found that Omega 3:6-essential fatty acids (EFA) supplementation improved manifestations of ADHD as well as reading and spelling in children with Developmental Coordination Disorder, reading disorders, and associated ADHD symptoms, without affecting motor coordination (250). Other studies have failed to show any benefit from Omega-3 supplementation (251). For review see (252).

Low serum ferritin has been correlated with baseline inattention, hyperactivity, and impulsivity, and also with the dose of amphetamine required to optimize clinical response, indicating that iron supplementation may be worthy of further exploration. Some studies have also shown benefit in ADHD from zinc supplementation (192).

18.1.9.4. Prevention

Considering the vast implications of ADHD for the individual as well as for society, and the fact that a good deal is known about risk factors for ADHD, it is surprising that very little emphasis is placed on prevention. Addressing the socioeconomic adversity within which ADHD and other neurobehavioral disorders flourish is a challenge to public health and political institutions.

However, the practitioner in primary care as well as the mental health provider who deals with children, parents, and women of childbearing age has the opportunity and obligation to inform about prevention, early intervention, and steps that can be taken to modify known genetic and environmental risk factors, as well as to treat manifest developmental and mental disorders. Prevention should address prepregnancy and pregnancy physical health, optimize chronic illness management, stress avoidance of toxins (i.e., smoking, lead, alcohol, mercury), and emphasize optimal nutrition. Essential fatty acids (EFAs) occupy a special role because they are essential for fetal neurodevelopment, may be protective for mood disorders, but are seriously deficient in the average American diet, which provides only 20–60% of the recommended daily dose. Mental health factors frequently are interactive with physical factors, and depression, isolation, and psychosocial stress contribute to adverse pregnancy outcome and fetal neurodevelopmental problems. Postnatal preventive measures again include optimal nutrition for the infant, child, and lactating mother, and enabling and maximizing caretaker-child responsiveness and interaction. This includes early recognition and treatment of postpartum depression and of the overall high incidence (20%) of maternal depression. Anticipatory guidance includes supporting the parent's understanding of the infants and child's developmental needs and capabilities, and addressing ADHD in parents and other family members. Early interventions for developmental and behavioral problems should be encouraged rather than adopting a "wait and see" attitude. Avoiding active and passive TV and video exposure during the first 2 years and limiting it afterwards, as recommended by the American Academy of Pediatrics, promoting social and physical activity, and providing parental and caretaker responsiveness may not eliminate ADHD, but provide the background for optimal emotional and cognitive development within the constraints of genetic predispositions, and mitigate the risk for development of psychiatric comorbidities.

In the child that is at high risk for or has manifest ADHD, supportive interventions are important for improving self-esteem and peer and family relationships, which can buffer the negative effects of ADHD on psychosocial functioning. Peer friendships, extracurricular activities (sports, arts, scouting, etc.), social-altruistic engagement, and parent involvement in school activities improve self-esteem and self-concept. An adult mentor outside of the nuclear family ("Big Brother/Sister", teacher, godparent, etc.) can be crucial especially for adolescents and especially in families that have multiple risk factors (253). Family activities and rituals, as well as stable daily routines help to provide the external emotional and temporal stability that is often very fragile in children with ADHD.

18.2. Oppositional Defiant Disorder (ODD)

ODD is one of the most commonly encountered clinical disorders in children and adolescents, characterized by a persistent pattern of angry or irritable mood, argumentative or defiant behavior, and vindictiveness that exceeds behavioral expectations for the individual's developmental level, gender, and culture. The severity of the disorder is linked to the pervasiveness of the behaviors across multiple settings.

18.2.1. Epidemiology

Prevalence studies have indicated a rate of 1–16%, depending on criteria and assessment methods used, with an average of 3.3%. There is a slight predominance in boys, with a male-female ratio of 1.4:1 prior to adolescence. Prevalence is consistent across cultural and ethnic groups, and onset is usually by age 8 (254).

18.2.2. Etiology

There is no unifying theory of etiology for ODD. High levels of emotional reactivity and poor frustration tolerance are temperamental factors associated with development of ODD. Harsh, inconsistent, and neglectful parenting practices are often implicated in causal theories. Neurobiological markers have not successfully distinguished ODD from Conduct Disorder. Baseline underarousal has consistently been found in youth with ODD, and exogenous biological factors may be implicated. Attachment theorists have suggested that oppositional behavior can develop in the face of an unresponsive parent. Aggressive children underutilize pertinent social cues, misattribute hostile intent to peers, generate fewer solutions to problems, and expect to be rewarded for aggressive responses. Although environmental factors such as poverty, lack of structure, and community violence have been posited as contributing factors; in fact, socio-economic status appears to be responsible for <1% of variance. However, intrafamilial social processes such as lack of parental supervision, lack of positive parental involvement, inconsistent discipline practices, and outright child abuse have been consistently implicated in the pathogenesis of disruptive behaviors (255).

18.2.3. Comorbidities

About 14% of children, adolescents, and adults with ODD also meet criteria for ADHD; 14% have a comorbid anxiety disorder, and 9% have comorbid depression (256). Persons with predominantly angry/irritable mood symptoms are at increased risk for mood disorders, while predominantly defiant/vindictive individuals frequently progress to conduct disorder. Learning disabilities, language disorders, and substance use disorders are also considered common comorbidities, although specific numbers are lacking. Oppositional behavior is sometimes used to manage anxiety, and is also frequently observed in autism spectrum disorders (255).

18.2.4. Prognosis

Approximately 67% of children will no longer meet criteria for diagnosis after 3 years. Early onset of symptoms is associated with worse prognosis, and 30% of these children progress to conduct disorder. Comorbidity with ADHD confers worse prognosis, with a greater range and persistence of problem behaviors, higher rates of peer rejection, and worse academic performance.

18.2.5. Treatment

18.2.5.1. Parent Training

The greatest degree of evidence supports parent management strategies targeting social skills, conflict resolution, and anger management, and training to improve parents' ability to handle disruptive behavior (257). The basic principles include: (1) reduce positive reinforcement of disruptive behavior; (2) increase reinforcement of prosocial and compliant behavior; (3) apply consequences for disruptive behavior; (4) make parental response predictable, contingent, and immediate. These interventions address the coercive response to parental demands and ways parents unwittingly reinforce the child's noncompliance (258).

18.2.5.2. Other therapies

Evidence supports programs such as Head Start, home visitation to high-risk families, and school-based programs as having a modest preventative effect for ODD (255). For severe cases, day treatment and residential treatment facilities may be necessary, always giving preference for the least restrictive treatment setting. Short-term, "inoculation" interventions (such as "boot camps") have not been shown to be effective and can even reinforce a fear-aggression reaction if children are exposed to frightening situations without providing behavioral alternatives (255).

18.2.5.3. Role of Medication in ODD

In the event of comorbid ADHD, treatment with stimulants or nonstimulants may improve oppositional behavior. Both typical and atypical antipsychotics have been shown to be helpful for treating aggression (259).

18.3. Intermittent Explosive Disorder

Intermittent Explosive Disorder, or IED, consists of a pattern of aggressive outbursts that typically last for only a few minutes and can involve either frequent (i.e., twice weekly) verbal or nondestructive physical aggression, or at least three outbursts of aggression that result in property destruction or physical injury over the course of a year. The outbursts are impulsive (rather than premeditated), usually come "out of the blue" or in response to a minor provocation, and appear grossly out of proportion to the alleged trigger (260).

Five to seven percent of the US population is estimated to display recurrent, problematic, impulsive aggression (261). Age of onset is typically in adolescence, and the course of the disorder tends to be relatively stable for up to two decades. Research has identified serotonergic abnormalities, especially in the anterior cingulate and orbitofrontal cortex, with higher amplitude amygdala response to anger stimuli on fMRI than in controls (260). There appears to be a higher prevalence in first-degree relatives (32%) and twins, suggesting a substantial genetic influence for impulsive aggression (262). Significant psychological correlates have also been found, with affected individuals demonstrating elevated relational aggression, more hostile attribution bias, greater affective lability and affective intensity, and a greater degree of immature defense mechanisms such as acting out, dissociation, projection, and rationalization. A history of trauma, especially in childhood, is frequently elicited (260).

The disorder is frequently comorbid with mood, anxiety, substance use, and personality disorders, as well as being frequently seen in individuals with ADHD (17.2%), ODD (21.6%), or Conduct Disorder (19.3%) (260). An IED diagnosis is not compatible, however, with a diagnosis of Disruptive mood dysregulation disorder, which always has onset in childhood and is characterized by a persistently negative mood state, not just during aggressive outbursts.

Preliminary medication trials with fluoxetine, divalproex, or oxcarbazepine have all been shown to reduce impulsive aggression, as has CBT, although additional research is needed regarding treatment of this disorder (260).

18.4. Conduct Disorder

18.4.1. Definition

Conduct disorder consists of a constellation of symptoms whereby rights of others are repeatedly violated. This comprises serious aggressive and antisocial behaviors such as bullying, initiating physical fights, physical cruelty to people and animals, fire setting and deliberately destroying others' properties, stealing, and serious violations of parental and school rules. This disturbance in behavior causes clinically significant impairment in social, academic, or occupational functioning.

18.4.2. Epidemiology

Three to five percent of preadolescent boys and 6–8% of adolescent boys meet criteria for conduct disorder. Boys outnumber girls 4:1 prior to adolescence to about 2:1 in adolescence (263). The Ontario Child Health Study indicated that for ages 4–16 years, 5.5% suffered from conduct disorder. Life-course persistent (LCP) versus adolescence-limited antisocial behavior are two examples of developmental pathways to antisocial or violent behavior.

LCP accounts for 5–8% of the offender populations which have an early onset involving serious crime and continue into adulthood. Twenty-five percent of adolescence-limited offenders continue their delinquent behavior into adulthood. These late starters may offend with peers but behave well in school and at home (264).

DSM-5 distinguishes between three subtypes of conduct disorder based on the age of onset. In childhood onset type, there is onset of at least one criterion characteristic of conduct disorder prior to age 10 years. These children begin showing mild conduct problems as early as preschool or early elementary school and their behavioral problems tend to increase in rate and severity throughout childhood and into adolescence.

The second type is the adolescence-onset conduct disorder in which there is absence of any criterion characteristic of conduct disorder prior to age 10 years. These youth do not show any significant behavioral problems in childhood. It is with the onset of adolescence that they begin to exhibit significant antisocial and delinquent behaviors.

Unspecified onset can be used when criteria for conduct disorder are met, but there is not enough information to determine if symptom onset was before or after 10 years of age.

Additional specifiers indicate a lack of prosocial emotions, such as remorse or guilt, lack of empathy, lack of concern about performance, and shallow or deficient affect.

18.4.3. Genetics

The Iowa Adoption cohorts have demonstrated that the degree of adoptee aggressiveness and conduct disorder has a significant genetic component. Cadoret et al. (265) followed the lead that the neurotransmitter serotonin or polymorphisms in the serotonin transporter gene (5HTT) were important sources of variability in "externalizing" behaviors such as aggression, conduct disorder, and attention deficit hyperactivity disorder. They genotyped a subgroup of adoptees ($n=87$) at high risk of these disorders with respect to the serotonin-transporter-linked promoter region (5HT-TLPR) polymorphism and used ordinal logistic regression to conduct an associated study. One type of interaction with the long variant of 5HT-TLPR increased externalizing behaviors in individuals with antisocial biologic parentage. A second interaction with one or more 5HT-TLPR short variants appeared to increase externalizing behaviors in conjunction with a genetic diathesis for alcoholism. It was also demonstrated that male individuals with a short variant were more likely to have higher symptom counts for conduct disorder, aggression, and ADHD. Their results supported the hypothesis that gene-biological family history interactions are involved in the externalizing behaviors studied.

Dick and colleagues (266) did a genome-wide screen for genes influencing conduct disorder. Their results suggest that regions on chromosomes 19 and 2 may contain genes conferring risk to conduct disorder. Interestingly the same region on chromosome 2 has also been linked to alcohol dependence in this sample (266). Childhood conduct disorder is known to be associated with the susceptibility for future alcohol problems. These findings suggest that some of the genes contributing to alcohol dependence in adulthood may also contribute to conduct disorder in childhood.

18.4.4. Risk Factors

There are several risk factors that contribute to the outcome of conduct disorder (267). Genes and intergenerational transmission and familial aggregation of antisocial behavior play a part in the development of conduct disorder. Studies have shown that there is an aggregation of disruptive and antisocial behaviors in families. It has also been demonstrated that a history of parental antisocial behavior disorder is associated with a preadolescent onset of conduct disorder. Cortisol levels were lower among sons of fathers with a childhood history of conduct disorder that progressed to antisocial personality disorder than those without a history. Testosterone has also been associated with aggression, including the early onset of aggression (267).

There is a link between underarousal of the autonomic nervous system and conduct disorder. Evidence has shown an association between low heart rate and conduct disorder and higher heart rate and anxiety, also seen in girls. A higher skin conductance has been found in individuals who avoid criminal behavior despite a paternal history of criminality. It has been hypothesized that these are markers of anxiety that play a role in inhibiting children from engaging in disruptive or criminal behavior (267).

Maternal smoking has also been linked to conduct disorder in boys, particularly with onset before puberty. Parent substance abuse, pregnancy, and birth complications have also been linked to disruptive behavior disorders. High levels of environmental toxins, such as lead, have been associated with greater parent and teacher ratings of aggressiveness, delinquency scores, and greater somatic complaints.

It has been seen that by adolescence, delinquent peers contribute greatly to the spread of delinquency and antisocial behaviors. Youth with conduct disorder are frequently rejected by prosocial peers and they tend to become more attached to youth with longer criminal histories. Males are more likely to be arrested for violent crimes and females for truancy, prostitution, running away, or underage drinking (264).

Potential links have been identified between temperament, antisocial behavior, and conduct disorder. Two temperamental types have been found. Type 1 is the callous unempathetic type, which appears to be unrelated to parenting and family context. Type 2 is the reactive, externalizing, antisocial child and is often associated with conduct disorder and negative parenting (268).

A modest to moderate link has been suggested between empathy and prosocial behavior. Boys and girls with conduct disorder are lower in empathy and the identification of interpersonal cues than those without conduct disorder.

Low IQ is associated with low achievement and school failure, both of which are related to later antisocial behavior. High verbal IQ was related to a decrease in conduct disorder symptoms over time only for boys in a clinic-referred sample without a parent with antisocial personality disorder (267).

Reading disorder may be associated with abnormal language processing within the left temporal cortex and has been linked to conduct disorder (267).

There has been a strong association between poverty and crime and disruptive behaviors. Disruptive behaviors among both boys and girls have been linked with poor and disadvantaged neighborhoods. Several other community factors are predictive of later violence such as availability of drugs, exposure to violence, and low SES. Youth in late adolescence with conduct disorder reported experiencing greater stress and engaging in more maladaptive coping strategies (267).

18.4.5. Protective Factors

Findings have indicated that outcomes are mediated by the interaction between protective elements and risk factors. Protection against antisocial behaviors is determined by high IQ, easy temperament, the ability to relate well to others, good work habits at school, areas of competence outside school, and a good relationship with at least one parent or other important adult. A school atmosphere that fosters success, responsibility, and self-discipline as well as selection of a nondelinquent peer is vital in protecting against continuing criminal activity (269).

18.4.6. Neurobiological Findings

Many previous brain-imaging studies in adults with antisocial behavior have shown functional and morphologic brain abnormalities. Sterzer et al. (270) used functional magnetic resonance imaging to test whether the impaired emotional responsiveness of adolescents with antisocial conduct disorder would be reflected by abnormal neural responses to negative affective stimuli. They compared brain activations in response to passive viewing of affect-laden pictures in conduct disorder patients to those in normal control subjects. The main effects for negative-neutral affective valence included activations in the amygdala and hippocampus, ventral extrastriate visual cortex, and the intraparietal sulcus bilaterally.

Kruesi et al. (271) compared regional brain volumes from magnetic resonance imaging scans from 10 youths with early onset conduct disorder and 10 healthy controls to determine whether prefrontal or temporal lobe brain volumes differed in the two groups. Results showed that subjects with conduct disorder had significantly reduced right temporal lobe and right temporal gray matter volumes. The prefrontal volumes in subjects with conduct disorder were 16% smaller than in controls, but the

difference did not reach statistical significance. It was also seen that early onset conduct disorder without substance abuse comorbidity was also significantly associated with small right temporal gray matter volumes.

Bussing et al. (272) conducted a study to examine a community sample of 12 children with combined subtype ADHD (ages 8–12 years, 7 with conduct disorder) and 19 healthy controls matched for age, gender, handedness, and poverty. Measurements of the left and total posterior, superior, and inferior lobes of the cerebellar vermis indicated smaller volumes for both pure ADHD and comorbid children compared to the controls. The results suggested ADHD and ADHD comorbid with conduct disorder have similar cerebellar morphology.

18.4.7. Treatment

It has been seen that no single intervention is effective against severe conduct disorder. Each dysfunctional domain needs to be targeted by multimodal interventions and this treatment must be delivered long enough to make a difference. Programs such as Head Start may help prevent delinquency in conduct disorder in preschool-aged children where poverty, perinatal complications, maternal attachment problems, temperamental traits, and parental education are risk factors. Such programs provide children with stimulation, parents with education, and parental support in crisis (269).

In the treatment of conduct disorder in school-aged children, both parenting skills training and training for the child are effective. The intervention should be aimed for the child, the family, as well as the school.

Adolescence is a time when internal self-regulation assumes more importance. Henggeler's Mutisystemic Therapy treats adolescents with conduct disorder in their psychosocial environment and family interventions (269). Augmentation of treatment is done by targeting social skills, conflict resolution, and anger management.

The childhood-onset group of conduct disorder has a history of behavior problems early in development and is at risk for the most severe and aggressive pattern of behaviors in adolescence and adulthood. Early interventions that are comprehensive and target multiple risk factors are found to be more effective. Families and Schools Together (FAST Track) Program involves multiple component interventions such as: (1) Parenting interventions that teach parents appropriate behavior management skills, (2) helping children develop anger control and problem-solving skills using a cognitive behavior intervention, (3) helping teachers use more effective behavior management using classroom interventions, (4) academic tutoring, and (5) home visits to support family functioning (263).

18.4.7.1. Pharmacotherapy

Medications are recommended only for treatment of target symptoms and comorbid disorders. Mood stabilizers, typical and atypical antipsychotics, alpha agonists, and the stimulants have been found to be useful in the treatment of children and adolescents with conduct disorder. Findling et al found that aggressive children with conduct disorder may benefit from quetiapine (273). Lithium was found to be safe and efficacious for the short-term treatment of aggressive inpatient children and adolescents with conduct disorder. Haloperidol was also found to be useful but lithium was better tolerated than haloperidol (267).

Risperidone and methylphenidate were also found to be superior to placebo in treating conduct disorder. Although no studies have demonstrated their superior efficacy in conduct disorder, antidepressants, lithium carbonate, carbamazepine, and propranolol are used in clinical practice. Clonidine and guanfacine are often used for their effect on reducing aggression and impulsivity (267). Donovan et al. found divalproex to be an efficacious treatment for explosive temper and mood lability in conduct disorder (274).

There are clear indications for hospitalization in children and adolescents who exhibit potential for imminent risk to self or others and show aggressive behavior or imminent deterioration in medical status (269). Inpatient, partial-hospitalization and residential treatment should include therapeutic milieu, family involvement, individual and group therapy, vocational training, treatment of comorbid disorders, and ongoing coordination with school, social services, and the juvenile justice system.

18.5. Summary

The explosion of neurobiological literature on ADHD and the Disruptive Behavior Disorders reflects the complex, fluid, and often-contradictory manifestations of brain–behavior relationships. This complexity is enhanced further by the accumulating research demonstrating significant differences in manifestations according to age, cognitive status, gender, comorbidities, psychosocial context, and treatment response. There is an enormous degree of individual variation shaped by the transaction of biological and environmental factors, which again has major implications for prevention and diagnostic and therapeutic interventions. ADHD has a high, though polygenic, heritability, with clinical expression strongly mediated by environmental and

familial factors. ADHD and CD appear to be genetically distinct, whereas ODD evolves within the context of ADHD. ADHD demonstrates extremely high affiliations with other neurodevelopmental and mental disorders. Research has expanded the conceptualization of ADHD as a primary disorder of frontal-striatal cognitive systems to include affective and motor regulatory pathways and to question the validity and utility of "executive function" deficits as the sole core dysfunctions. ADHD manifests from early childhood and persists in most cases throughout the lifespan. Evaluation and management of the individual needs to acknowledge the co-occurrence of ADHD with learning disorders, anxiety, and mood disorders, which are the basis for the high degree of psychosocial morbidity. Despite the etiological, neuropsychological, and clinical complexity, psychostimulant treatment can help to attenuate some of the most detrimental psychosocial effects that occur when left untreated. Alternative drugs are available in patients who cannot use stimulants, and behavioral and psychosocial interventions should be included as supportive treatments, especially in young children. Prevention and early intervention are feasible, given that there are clear causal relationships, such as toxic exposures (prenatal exposure to smoking, alcohol, lead, etc.), parental psychopathology, and environmental and lifestyle stressors that can be eliminated or modified if appropriate intervention is sought and available.

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19
Mood Disorders in Children and Adolescents

Kathryn R. Cullen, M.D. and Ana Bortnova, B.A.*

Abstract Mood disorders are chronic, often debilitating illnesses that affect people of all ages. In children and adolescents, these disorders can be particularly difficult to address, as presentation, diagnosis, and treatment are often complicated and outcomes are uncertain. There are many proposed etiologies for the development of these disorders, including biological and psychosocial factors. Although research on treatment of depression in children and in adolescents lags behind that in adults, some evidence has emerged to support the use of validated treatments for mood disorders in youth. Research is needed to better understand the developmental etiology and mechanisms in pediatric mood disorders, which will guide advancement in pharmacologic and psychotherapeutic treatment for children and adolescents suffering from mood disorders.

Keywords Major depressive disorder • Bipolar disorder • Mood disorder • Children • Adolescents

Mood disorders in children and adolescents are serious, complicated disorders that impact psychological, social, and biological well-being. With significant morbidity and mortality, lengthy course, and risk for recurrence in adulthood (1, 2) these disorders can impair growth and development if not properly addressed. Mood disorders often interfere with family and peer relationships and with educational performance (3–5). These youngsters are also at increased risk for substance abuse, legal difficulties, and hospitalizations (6–8). Depressed children and adolescents are at increased risk for both suicide attempts and completed suicides (9, 10). The impact that mood disorders can have on children and adolescents requires measures aimed at the early detection and treatment. Thus, a basic understanding of mood disorders, their etiologies, and their treatments is essential to clinicians treating children and adolescents.

19.1. Diagnosing Mood Disorders in Children and Adolescents

The Diagnostic and Statistical Manual of Mental Disorders 5 (DSM-5) provides diagnostic criteria for each mood disorder. When applying these criteria to a patient it is crucial to consider the age of the patient, as methods of diagnosis may vary with age. For the most complete diagnosis, information should be obtained from various sources, such as the child's family, teachers, and physicians (11).

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K.R. Cullen, M.D. (✉)
Assistant Professor, Department of Psychiatry, University of Minnesota School of Medicine,
Minneapolis, MN, USA
e-mail: rega0026@umn.edu

A. Bortnova, B.A.
Research Assistant, Department of Psychiatry, University of Minnesota School of Medicine,
Minneapolis, MN, USA
e-mail: bortn005@umn.edu

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19.1.1. Major Depressive Disorder

The DSM-5 criteria for major depressive disorder include presence of either depressed/irritable mood or anhedonia as well as other depressive symptoms (failure to meet expected growth rate, insomnia, hypersomnia, changes in weight or appetite, lack of energy, thoughts of death or suicidal ideations, poor concentration, etc.) for two weeks (12, 13).

These symptoms must not be due to the effects of medication, alcohol or drug use, or a general medical condition. A major depressive episode is considered to have ended when the symptoms have diminished below the threshold for diagnosis or have been resolved completely for at least three consecutive months (12). In a departure from DSM-IV, the case of bereavement is no longer an exclusion for the diagnosis of MDD.

19.1.2. Persistent Depressive Disorder

Persistent depressive disorder, previously known as dysthymia, in children and adolescents is defined as the presence of a persistent depressed or irritable mood that occurs for most of the day, for a majority of days, and it is present for at least one year (12). The symptoms must result in clinically significant distress or impairment in functioning or require markedly increased effort to maintain a previous level of functioning. In addition, a major depressive episode may not be present during the initial year of symptoms.

19.1.3. Bipolar Disorders

For a diagnosis of a manic episode, DSM-5 requires presence of an irritable or elevated mood as well as increased energy and three or more of several other symptoms (grandiosity, pressured speech, flight of ideas, distractibility, decreased need for sleep, impulsivity) that last for one week. These symptoms cause social impairment and the episode should not be due to an abuse of a drug or a medical condition or treatment (12). Recent work examined six commonly-used research diagnostic interview instruments in the application of DSM 5 criteria for pediatric bipolar disorder, and found significant differences in the criteria and descriptive text for a manic episode. Galanter and colleagues noted that instruments varied with respect to whether symptoms must represent a change from the child's usual state, and whether B-criteria are required to co-occur with A-criteria (14). This issue may help explain some of the inconsistencies in findings across studies in pediatric bipolar disorder, and represents an important problem for the field to address moving forward.

Bipolar II disorder is characterized by one or more major depressive episodes accompanied by at least one hypomanic episode (similar to a manic episode but lasting at least four days) (12). Hypomanic episodes should include a minimum of three of the above-mentioned seven manic symptoms. A hypomanic episode is not severe enough to require hospitalization and does not cause a marked impairment in social or other important areas of functioning (11).

Cyclothymic disorder is a chronic and fluctuating mood disorder of milder clinical symptomatology and is characterized by multiple periods of mild hypomanic symptoms alternating with periods of mild depression (12). Hypomanic and depressive symptoms are both insufficient in number, severity, duration, and pervasiveness to meet full criteria for mania or depression. Symptoms must be present for at least one year and without a symptom-free interval longer than two months.

Children and adolescents who exhibit manic symptoms with mixed features who do not meet full criteria for the disorder (typically due to failure to meet the duration criteria for individual episodes) are frequently diagnosed as Bipolar Disorder, Not Elsewhere Defined. Notable efforts to examine pediatric bipolar disorder such as the Course and Outcome of Bipolar Youth (COBY) project have proposed criteria for diagnosing Bipolar NED. These include individuals who do not meet the DSM-5 criteria for BP-I or BP-II but have had a distinct period of abnormally elevated, expansive, or irritable mood plus the following: 1) two DSM-5 manic symptoms (three if the mood is irritability only) that were clearly associated with the onset of abnormal mood, 2) a clear change in functioning, 3) mood and symptom duration of a minimum of 4 hours within a 24-hour period for a day to be considered meeting the diagnostic threshold, and 4) a minimum of 4 days (not necessarily consecutive) meeting the mood, symptom, duration, and functional change criteria over the subject's lifetime, which could be two episodes lasting two days, four episodes lasting one day, or another variation (15). Recent work has suggested that the symptomatology and functioning of this group of children is very similar to children who meet criteria for Bipolar Disorder types I or II, supporting the hypothesis that these illnesses are on the same spectrum (16).

The diagnostic criteria for bipolar disorder used for adults may not always be reliable in diagnosing mania in children and adolescents (17), and the diagnosis of bipolar disorder in children has been especially controversial (18, 19). Unlike adults, children and adolescents often present with a delay in initial manic symptoms, or may actually begin with a subclinical presentation (7). In addition, children and adolescents often have an atypical presentation, including psychotic symptoms, suicide

attempts, inappropriate sexual behavior, behavioral symptoms and a "stormy" first year of illness (20, 21). The establishment of more developmentally appropriate diagnostic criteria has been suggested to provide more validity (22).

19.2. Etiology, Pathogenesis and Neurobiological Findings

19.2.1. Hormones

Several biological/hormonal factors have been implicated in the development of depression, i.e. growth hormone, cortisol, ACTH, prolactin, thyroid hormones, and melatonin. Also, differences in treatment responses to various medications with respect to age, suggest neurobiological mechanisms are involved in the course of the disease. However, the roles that such neurobiological factors play in the etiology of pediatric and adolescent mood disorders are not well understood.

Studies of depressed children have demonstrated hyposecretion of growth hormone after various chemical challenges, including insulin and growth hormone releasing hormone (GHRH) (23, 24). This dysregulation of growth hormone secretion is hypothesized to either reflect changes in the central noradrenergic receptors or be the result of alterations in transmitters, such as somatomedin or somatostatin. Growth hormone suppression has even been reported in children and adolescents who have never experienced an episode of major depression, but have a strong family history of mood disorders (25). Conversely, some studies in children (26) and adolescents (27, 28) have reported a relative hypersecretion of growth hormone during sleep. It has been suggested that this nocturnal hypersecretion may be affected by stressful life events (29). However, other studies have failed to replicate this finding (30). One case-controlled study comparing 44 adolescents with major depression and 37 non-depressed control subjects found no differences in nocturnal growth hormone secretion. However, when subjects in the depression group were divided into suicidal and non-suicidal groups, a significant blunting of nocturnal growth hormone secretion was present in the suicidal group compared with the nonsuicidal group (31).

Another study (32) examined the growth hormone response to growth hormone-releasing hormone (GHRH) in 82 depressed children compared to 55 controls, matched for age, gender, and pubertal status. The mean growth hormone response to the GHRH was significantly lower in the depressed group. However the mechanism behind this phenomenon is still unclear. The authors of this study discovered low growth hormone states persist, even after clinical recovery, which suggested growth hormone may function as a "trait marker" for depressive disorders (32).

Cortisol has also been implicated in the etiology of depression. The Hypothalamic-Pituitary-Adrenal (HPA) axis is involved in neuroendocrine and behavioral responses to stress, and is influenced by developmental factors and levels of social interaction (33). Animal studies of HPA axis reactivity can invoke the experience of social stress and can lead to behaviors similar to those seen in depression and anxiety in humans (34).

Studies of the HPA axis in depressed adults have found elevated cortisol levels (35). However, the relationship between HPA axis dysfunction and depression is less clear in children and adolescents. Some studies have reported no significant difference in baseline plasma cortisol secretion between depressed outpatient children (36) and adolescents (36) with non-depressed controls. Ryan et al. (1994) found lower cortisol levels in children suffering from early-onset major depressive disorder compared with nondepressed controls after an infusion of L-5-hydroxytryptophan, a serotonin precursor, suggesting an abnormality in cortisol regulatory mechanisms in some depressed children and adolescents (37). Other studies found severely depressed and suicidal children and adolescents manifest cortisol hypersecretion (38, 39). In a longitudinal study of adolescent depression, Rao and colleagues measured urinary cortisol in 55 adolescents with MDD during the index episode. Higher cortisol levels were associated with a longer time to recovery, and, in combination with recent stressful events, predicted recurrence. Social support moderated the effect of cortisol on the index episode and was protective against risk of recurrence (40). Depressed preschool-aged children also had cortisol irregularities when subjected to separation or frustrating stimuli (41). Explanations offered for the diverse findings in HPA axis reactivity in depressed children and adolescents include age, different maturation levels, decreased prevalence of melancholic symptoms, and more rapid adaptation to stress in depressed youth (42).

Corticotropin-releasing hormone (CRH) levels have also been an important area of study, as cortisol secretion abnormalities have been linked to alterations in endogenous CRH secretion (43). Adult studies have consistently demonstrated elevated baseline cortisol and blunted corticotropin secretion after CRH infusion (44). However, a comparison of pre-pubertal children with major depressive disorder and non-depressed control subjects did not find significant differences in baseline or post-CRH stimulation levels of either cortisol or ACTH (44).

Pineal gland irregularities and prolactin secretion may be altered in mood disorders. Studies in depressed adults found blunted prolactin secretion after administration of serotonin precursors and agonists (45). Waterman et al. (46) did not find a significant difference in basal 24-hour prolactin concentrations in adolescents with major depression compared with control subjects. A study exploring nocturnal secretion of various hormones in depressed children confirmed these findings and also found no significant difference in prolactin secretion between depressed children and controls (30).

Common thyroid abnormalities have been found in depressed adults, but many of these abnormalities did not result in overt thyroid disease (47). Thyroid aberrations in depressed adults include elevated basal thyroxine (T4), reduced triidothyroxine (T3) and thyroid-stimulating hormone (TSH), and blunted TSH response to thyrotropin-releasing hormone (47). However, thyroid studies in depressed children and adolescents are inconclusive.

One study (48) examined thyroid hormone concentrations in depressed adolescents and concluded that free T4 concentrations were lowered in depressed adolescents, which suggested a relationship between negative behaviors and dysfunction of the hypothalamic-pituitary adrenal axis. A similar study by the same group (48) explored thyroid function in depressed children and reported reduced basal T4, T3, and TSH values (48). However, reduced levels of T4 and TSH were only found in the male subjects. To date, no studies have evaluated TRH challenges in depressed and normal control adolescents.

19.2.2. Melatonin

A few studies have investigated the role of melatonin in pediatric MDD. A small study (49) found lowered nocturnal serum melatonin levels in depressed boys aged 7–13 years. Another study found depressed children and adolescents produced higher levels of overnight urine melatonin than those without primary major depression (50). A study exploring pineal gland function by measuring serum melatonin levels during both wakefulness and sleep in depressed children and adolescents found nocturnal serum melatonin levels significantly increased in subjects with major depression, and also demonstrated a significantly higher melatonin profile in those subjects with co-occurring psychotic symptoms (51). More recently, a study investigated circadian profiles in young people during the early stages of affective disorders in order to assess the progression of abnormalities. Maismith and colleagues reported that although there was no difference in the timing onset of melatonin across illness stages, it was noted that patients with established disorders, as opposed to earlier and attenuated syndromes, had more marked reductions in melatonin secretion, and that lower levels were associated with subjective sleepiness and poorer performance on neuropsychological tests of verbal memory (52).

19.2.3. Neurochemical Findings

19.2.3.1. Major Depressive Disorder

Norepinephrine and serotonin are the neurochemicals associated with the regulation of mood and the pathophysiology of depression. In addition, the neurotransmitter acetylcholine is believed to be involved in mood disorders, as drugs which increase its levels reportedly induce depressive symptoms in nondepressed adults and exacerbate depressive symptoms in patients with depression (53). The exact role of acetylcholine in mood disorders in children and adolescents is still unclear.

Antidepressants appear to function by restoring healthy functioning to dysregulated neurotransmitter systems in the brain (54). While serotonergic system dysregulation is demonstrated across the lifespan in depression, the nature of these neurotransmitter dysregulations appear to differ in children, adolescents, and adults. This is demonstrated in several ways, such as the difference of response to medications such as tricyclic antidepressants, which appear to be more effective in older populations (55).

19.2.3.2. Bipolar disorder

Manic symptoms such as flight of ideas, irritability, distractibility, and high energy have been linked to increased neuronal excitability from decreased activity of the Na^+-K^+-ATPase pump in bipolar disorder (56). Depressive symptoms in bipolar disorder are hypothesized to be secondary to a larger decrease in pump activity and a resultant decrease in neurotransmitter release (56). Guanine nucleotide binding proteins (57) have also been postulated to play an important role in the molecular etiology of bipolar disorder (58). This hypothesis is based on the finding that lithium attenuates the functioning of G-protein and dampens the oscillatory system, which promotes mood stabilization (59).

19.2.4. Sleep Abnormalities

Sleep abnormalities in depression have been studied in both pediatric and adult populations. However, results vary with age. Depressed children and adolescents frequently report sleep disturbances (60), but to date, EEG findings have not paralleled those in depressed adults. Studies in adults with major depression have consistently demonstrated increased rapid eye movement (REM) density in early REM periods, decreased delta (slow-wave) sleep; disturbed sleep continuity, and shortened REM

latency (61). Studies of depressed adolescents have reported prolonged sleep latency, reduced REM latency, and decreased sleep, but no differences in delta sleep (60, 62–65). Greater sleep changes in inpatient adolescents and in those with psychosis, suicidality, and endogenous major depressive disorder subtypes have been observed (62, 64, 66). A review of sleep studies of depressed children (55) found only one study that reported recordable sleep abnormalities in depressed children. This study reported decreased REM latency and increased sleep latency in an inpatient sample (67).

Sleep abnormalities may be a marker to signal future trajectories for mood disorder. Rao and colleagues conducted a sleep study in 28 adolescents with unipolar depression and evaluated them 7 years later (68), and examined whether sleep patterns could predict course of illness. Adolescents whose course of illness in the 7 year follow-up period was consistent with unipolar depression showed lower REM latency, higher REM density, and more REM sleep in the early part of the night compared to those who converted to bipolar and to normal controls who remained free of psychopathology at follow-up. Depressed adolescents who later developed bipolar disorder were distinguished by having more stage 1 sleep and diminished stage 4 sleep than the other groups. Additionally, a longitudinal study in adolescents at risk for depression by virtue of having a parent with depression showed that compared with normal controls, adolescents at high risk for depression had shorter latency to rapid eye movement (REM) sleep, increased phasic REM sleep, and more REM sleep at baseline (69). Shorter REM latency, higher REM density and elevated nocturnal urinary free cortisol (measured at baseline) were associated with the development of depression during the 5-year follow-up.

19.2.5. Genetic Factors

19.2.5.1. Major Depressive Disorder

Depressed children and adolescents commonly have family members affected by mood disorders. The reported lifetime risk of major depressive disorder in children of depressed parents ranges from 15% (70) to 45% (71). Twin studies have supported the presence of a genetic factor in the etiology of depression, with higher concordance rates for depression in monozygotic (54%) versus dizygotic (24%) twins (72). Recurrence and an early-onset of symptoms have been suggested as characteristics most associated with familial risk (72). In fact, lifetime rates of mood disorders in first-degree relatives of depressed inpatient adolescents are significantly higher than in the general population (73). In addition, first degree-relatives of depressed suicidal adolescents may have increased lifetime rates of suicidal behavior (74). Several studies report children of depressed parents are at high risk to develop depression, and have increased risk for other psychopathology, including anxiety and disruptive disorders (11).

Relatives of patients with bipolar disorder are also at risk for major depression, as relatives of bipolar probands have higher rates of unipolar depression as well as bipolar disorder (75). In addition, a familial relationship has been suggested between major depression and bipolar type II disorder. However large-scale studies to explore this relationship to date are lacking (72).

Familial studies report a strong risk for the development of depression in the children of depressed parents, particularly if the history of depression extends to previous generations (76). There is evidence to suggest a genetic component to the development of major depression (77). However, recent studies suggest environmental stressors may be an important factor in the development of depression in genetically-predisposed individuals (78–80).

Genetic research has increasingly sought to examine not only how genes are associated with various mental health disorders, but how genetic and environmental factors interact to shape an individual's outcomes. This theory, known as gene-environment interaction (G X E), suggests that the effect of the environment on an individual's outcome depends on their genes and vice versa (296). One of the most studied genes in the depression literature is the serotonin-linked polymorphism, 5-HTTLPR. In a seminal paper, Caspi et al. (298) reported that individuals with the short allele of the gene were more likely to develop depression in the face of stressful life events than individuals with two long alleles of the gene. More recently, Vrshek-Schallhorn et al. (297) studied this gene and life events in adolescents and young adults, and found that there was a significant G X E effect for interpersonal life stressors as opposed to non-interpersonal life stressors for carriers of the short (S) genotype of 5-HTTLPR. Similar investigations have been conducted examining different polymorphisms of the brain-derived neurotrophic factor (BDNF); for example Cruz-Fuentes and colleagues recently reported that early life adversity raises risk for depression only in those with the val-val allele for this gene (300). Other studies have looked at various other genes and their prevalence in individuals with MDD. Periera et al. (299) examined the genetic variation of the AKT1 and AKT1P genes, which play an important role in down-stream signaling pathways relevant to serotonin systems and mood, in late-onset depression. They found that there is a strong association for one of the polymorphisms of the AKT1 gene with late onset depression (LOD). However, these genes have not yet been examined in early-onset depression. More recently, the field has increasingly recognized that MDD is a complex, polygenetic

disorder, and there has been interest in examining the entire genome to identify risk for MDD. Unfortunately, however, studies utilizing genome-wide association techniques of large samples have failed to yield supporting evidence for the candidate gene studies (i.e. 5HTTLPR, BDNF), and have yet to reveal any conclusive information on the genetics of MDD (301).

19.2.5.2. Bipolar Disorder

With an estimated heritability of 85–89%, bipolar disorder has a strong genetic component (75). Family studies of adolescent-onset bipolar patients found bipolar disorder was increased among first-degree relatives (81). In addition, an early onset of disease predicts a higher prevalence of illness in family members (82). Post et al. (302), who studied this relationship between family members and early onset of bipolar disorder, found that individuals in the United States, compared to Europe, had a higher likelihood of having two parents with bipolar disorder and therefore were more likely to develop bipolar disorder at an earlier age.

Similar to unipolar depression, the genetic basis for bipolar disorder is likely to be the cumulative effect of many genes (83), which leave a person susceptible to environmental influences and stressors which can lead to the development of bipolar disorder. Although different genes may be involved from family to family, the same phenotypic mood disorder may result (83).

Several candidate genes have been investigated and replicated in bipolar disorder, including *SLC6A4/5-HTT* [*serotonin transporter gene*], *BDNF* [*brain-derived neurotrophic factor*], *DAOA* [*D-amino acid oxidase activator*], *DTNBP1* [*dysbindin*], *NRG1* [*neuregulin 1*], *DISC1* [*disrupted in schizophrenia 1*]) (303). Additionally, genome-wide association studies have indicated polymorphisms in two genes (*CACNA1C [calcium channel, voltage-dependent, L type, alpha 1C subunit]*, and *ANK3* [*ankyrin 3*]). Therefore, in contrast to MDD, recent progress has been made in bipolar genetic research, identifying several common, single nucleotide polymorphisms that have survived significance testing in genome-wide analyses (304). However, these discoveries have not yet been translated to clinical practice (e.g. genetic testing to determine risk for bipolar disorder in the clinic.)

19.2.6. Neuroimaging Abnormalities

19.2.6.1. Major Depressive Disorder

The past two decades have seen a major advance in the understanding of depression through the use of brain imaging research. Various modalities including structural, functional, and magnetic resonance spectroscopy, and imaging studies in depressed adults have implicated a network of brain regions referred to as fronto-limbic neural circuitry (84). This network encompasses both dorsal and ventral frontal areas, the anterior cingulate cortex, the amygdala, the hippocampus, and the insula, which are known to mediate processes relevant to emotion and mood (85). The areas in this network are known to undergo significant change and development throughout adolescence (86, 87). Although lagging significantly behind research in adult depression, some important strides have been made using neuroimaging techniques in pediatric depression. These studies have generally supported adult work implicating fronto-limbic neural circuitry, and they suggest that the pathophysiology of depression may involve an abnormality in the development of these networks (88).

19.2.6.2. Bipolar Disorder

Similar to the research in MDD, neuroimaging studies in pediatric bipolar disorder have generally implicated fronto-limbic neural circuitry (89, 90). Emerging longitudinal research examining youth with bipolar disorder has begun to suggest progressive changes that occur across development, including loss in gray matter volume in prefrontal, anterior cingulate, and subgenual cortical regions (91). Whereas increased amygdala volumes has been an important finding in adults with bipolar disorder, the opposite pattern has been found in children (92–94), and recent work has suggested that amygdala volume is reduced at the onset of illness and increases with age (95).

19.3. Psychological Theories of Mood Disorders

19.3.1. Learned Helplessness

Seligman and Peterson's (97) learned helplessness model theorizes that depression is connected to the experience of uncontrollable life events. These uncontrollable life events lead the person to perceive his or her behavior as independent from these events. Thus, the person essentially "gives up." This idea of helplessness is associated with motivational, cognitive, and emotional deficits in human responsiveness.

19.3.2. Cognitive Models

Cognitive models provide a theory that account for the thoughts, or cognitions associated with depression. In Beck's (98) model, distorted, negative thoughts characteristic of depressed individuals are seen as underlying depression.

19.3.3. Social and Environmental Factors in the Development of Mood Disorders

Social and environmental factors may have a role in the development and maintenance of mood disorders. Children and adolescents with mood disorders typically have poor relationships with parents, siblings, and peers (96). In the family, factors such as lack of parental affect, irritability directed toward the child, and child abuse may also contribute to increased vulnerability to depression in the child (99). In regards to mania, when child rearing practices of manic parents were examined, many had poor parenting techniques (100). The episodic nature of the unreasonable behavior of these manic parents may be harmful to the normal development of children, especially children with mood disorders (17).

19.3.4. Attachment theory

In his attachment theory, Bowlby emphasized the importance of early relationships with caregivers for development and relationships formed later in life (101). Mary Ainsworth developed the Strange Situation, a paradigm designed to allow characterization of parent-child relationships as either secure or insecure attachment (102). Disruptions in attachment have important implications for the later development of psychopathology (103).

19.4. Epidemiology

19.4.1. Depressive Disorders

It is estimated that approximately 2.5% of children and 8.3% of adolescents in the United States have depressive disorders (1). However, no large-scale epidemiological studies have been done on the prevalence of major depressive disorder in prepubertal children to date (11). In specialized populations, depression was reported in 7% of children admitted to pediatric hospitals for medical reasons (104) and in 40% of children in pediatric neurology clinics presenting with headaches (105). In prepubertal children, depression occurs at approximately the same rate in both sexes (2). However, after puberty there is a marked difference in the sexes, with females presenting with major depression twice as frequently as males. The lifetime prevalence rate of depressive disorders in adolescents has been estimated to range from 15 to 20%, which is comparable to the lifetime rate of major depressive disorder in adults (106). An epidemiological study reported prevalence rates of persistent depressive disorder of 1.6% to 8.0% in adolescents (107).

19.4.2. Bipolar Disorders

Bipolar disorder does not occur as often in the general population as major depressive disorder or persistent depressive disorder. The lifetime prevalence of bipolar disorder approaches approximately 1% by adolescence (7). Geller et al. (1998) reported the mean age of childhood-onset bipolar disorder as approximately eight years (108). Burke et al. (109) found the age of onset to be slightly older at 15 to 19 years. Patients with early-onset bipolar disorder have higher rates of psychotic features and a more severe course of illness than those with an older age of onset (110–112). Children and adolescents with bipolar disorder have a more prolonged course and have decreased response to treatment (8, 111).

19.5. Clinical Presentations and Phenomenology

19.5.1. Depressive Disorders

Young children, unable to express emotions like adults, present with more somatic complaints, psychomotor agitation, and mood-congruent hallucinations (11). With increasing age, these symptoms lessen, but self-esteem may worsen. Adolescents, as a result, can present with antisocial behavior, substance use, restlessness, "grouchiness," aggression, social withdrawal, family and school problems, wanting to leave home, or feelings of not being approved of or understood. Later in adolescence, the phenomenology of major depression more closely approximates adult major depression (113). It has been suggested that

symptoms of "endogenicity" – melancholia, psychosis, suicide attempts, lethality of suicide attempts, and functional impairment – increase with age (1).

19.5.2. Bipolar Disorders

Bipolar disorder also presents with variability at different stages of development. Younger, pre-school aged children often present with explosive and unmanageable temper tantrums, sexual joking, and nightmares with violent imagery (1). As children become school-aged, they begin to display pressured speech and increased motor and goal-directed activity, involvement in pleasurable activities with a high level of danger, hypersexuality, disordered sleep patterns with high activity levels in the bedroom before sleep (114). However, at this age, manic episodes may not be the discrete periods often seen in adults, and often have a chronic, non-episodic, and rapid-cycling presentation (115, 116). Irritable, unpredictable and labile moods are common in adolescents and may be more common than euphoria in this age group (11).

19.6. Gender Differences in Mood Disorders

19.6.1. Depressive Disorders

An interesting phenomenon noticed in depression after puberty is the dramatic shift of occurrence, leading to a female-to-male ratio of depression of 2:1 (2). Biologically, several changes have been implicated in the gender differences observed in depressed adolescents; however, evidence-based literature in this area is quite limited. One theory involves the increased oxytocin production observed in post-pubertal females (117). Changes in hormones such as progesterone, estrogen, and cortisol have also been implicated in the differences observed between the genders in depression. There is also evidence in the adult literature to suggest that gender may affect response to medications, specifically SSRIs (118), but studies to date in this area have been inconclusive (119) and largely unexplored in pediatric populations.

19.6.2. Bipolar Disorders

Gender differences in bipolar disorder are even less studied. There is no evidence to date to suggest a gender difference in the development and treatment of bipolar disorder in children and adolescents. Pre-pubertal onset mania may be more common in males than in females, particularly in hospitalized patients (108).

19.7. Differential Diagnoses/Comorbidities

19.7.1. Major Depressive Disorder

The most frequent comorbid diagnoses with major depressive disorder are persistent depressive disorder (30%-80%), anxiety disorders (30%-80%), disruptive disorders (10%-80%), and substance abuse disorders (20%-30%) (11). In general, comorbidities with major depressive disorder are associated with a more severe and persistent course of depression (1). Thus, it is important to assess comorbid psychiatric diagnoses as they may influence treatment and have an impact on the course of depression. The comorbidity of MDD and anxiety disorders can have important clinical implications; individuals with both disorders may have increased risk for substance abuse, suicidality, poor response to psychotherapy, and psychosocial problems. Anxiety disorders comorbid with MDD present differently at different stages throughout childhood. Separation anxiety is most common in children whereas generalized anxiety disorder is most common in adolescents (120).

Conduct disorders are also common in children. They may be present in 15–30% of depressed children and adolescents (121). More than 50% of children and adolescents with a mood disorder have conduct disorder or oppositional defiant disorder (11). Symptoms of conduct disorder such as irritability, oppositional defiance and social withdrawal may mask MDD symptoms (120). Youth with both MDD and conduct disorders are at increased risk for suicide (122). Although comorbid conduct disorder and MDD in childhood is not associated with increased risk of MDD in adulthood (120), depressed patients with comorbid conduct disorders had worse short-term outcome, fewer melancholic symptoms, fewer recurrences of depression, a lower familial aggregation of mood disorders, a higher incidence of adult criminality, more suicide attempts, higher levels of family criticism, and an increased response to placebo than patients with only MDD (11).

Substance abuse is also a common comorbid diagnosis in adolescents with MDD (1). Rao et al. found depressed adolescents had an earlier onset of substance use disorders and greater psychosocial impairment than control subjects (123).

Comorbid obsessive-compulsive disorder (OCD) occurs in 10–30% of children and adolescents with MDD. Severe OCD symptoms require treatment. However, they should be addressed after the treatment of the depressive symptoms, as mood disorders can interfere with a patient's motivation and compliance with behavioral therapy programs (120).

Several diagnoses included in the differential diagnosis of MDD should be ruled out. For instance, adjustment disorder with depressed mood is a possibility in a school-age child with a depressed affect. In this diagnosis, several depressive symptoms are present, but there are not enough present to warrant a diagnosis of MDD, and the duration is less than 6 months (96). Another important diagnostic consideration (especially in adolescents) is substance-induced mood disorder with depressive features. This diagnosis is made when the depressed mood is due to the physiological side effects of a medication, drug of abuse, exposure to a toxin, or other somatic treatment (11). A substance-induced depression can be distinguished from a major depressive disorder by the onset, course, and clinical presentation of the disorder (123). It is also important to consider all medical conditions that may produce psychiatric syndromes similar to MDD or DD (96).

19.7.2. Bipolar Disorder

A diagnosis of mania should not be made until the child or adolescent is observed in a drug-free state. Medications reported to induce manic states include amphetamines, corticosteroids, sympathomimetics, isoniazid, and antidepressants (17). Hyperthyroidism may present with a manic-like state (17). Neurological conditions also may cause a manic syndrome such as head trauma, multiple sclerosis, stroke, and seizure disorders with a left temporal focus (17). Space occupying lesions such as meningiomas, gliomas, and metastatic lesions in the thalamus have been implicated (124).

There are also psychiatric disorders that can co-occur with or be incorrectly diagnosed as mania. For instance, Attention-Deficit/hyperactivity disorder (ADHD) and Bipolar Disorder are difficult to differentiate in children and adolescents (125). Specifically, psychomotor agitation, distractibility, aggression, poor school performance, restless sleep, and sexually inappropriate behavior are symptoms of both ADHD and Bipolar Disorder. Manic children, however, have more affect and are euphoric or irritable. Children with ADHD have low self-esteem and a much longer duration of symptoms (17). It has been suggested that childhood-onset bipolar disorder is frequently comorbid with ADHD (126). Whereas hyperactivity, impulsivity and attention impairments are present in both groups, the presence of episodes of prolonged elevated mood and of a decreased need for sleep differentiates juvenile-onset Bipolar Disorder from ADHD (127).

Conduct disorder is also frequently comorbid with Bipolar Disorder (128). Many children with mania have unruly, disruptive behavior suggestive of a conduct disorder. However, children with a "pure" conduct disorder do not have pressured speech, flight of ideas, or delusions of grandeur (17). Children and adolescents with bipolar disorder sometimes become involved with the use of alcohol or drugs in an attempt to treat symptoms of their mood disorder. Most adolescents have easy access to drugs and alcohol (17).

Schizophrenia may also be confused as a manic episode because of the presence of delusions and hallucinations in both disorders (17). Psychotic symptoms are common in prepubertal manic children (114). Usually the course of illness can help distinguish these diagnoses: the onset of schizophrenia is typically insidious and the onset of a manic episode is usually acute (17).

Sexual abuse is also important as a differential diagnosis in childhood because manic hypersexuality is often manifested in children by self-stimulatory behaviors, including masturbation in public (11). Therefore, it is important to evaluate for sexual abuse and exposure to inappropriate adult sexual behaviors when considering the diagnosis of bipolar mania (124).

19.8. Treatment

The treatment approach to child and adolescent mood disorders should be biopsychosocial and include psychotherapy, medication, educational assessment and planning, and social skills training (13). Treatment setting is also a consideration. It must be determined if the patient may be treated appropriately on an outpatient basis. Hospitalization may be required to protect the child or adolescent from either his/her own dangerous behaviors or to protect him/her from a volatile and unsafe home environment. Aggression, deterioration in symptoms or functional status, and family unrest are the major predictors of inpatient hospitalization of children and adolescents (129, 130).

19.8.1. Biological and Pharmacological Treatments

19.8.1.1. Major Depressive Disorder

19.8.1.1.1. Selective Serotonin Reuptake Inhibitors

There are seven randomized controlled trials exploring the use of selective serotonin reuptake inhibitors (SSRIs) in the acute treatment of MDD in children and adolescents. These include three randomized controlled trials of fluoxetine in children and adolescents ages 7–18, depending on the study (131, 132); one randomized, controlled study of paroxetine, placebo, and imipramine in adolescents ages 12–18 (133); one multicenter randomized, double-blind, placebo-controlled trial of sertraline in children and adolescents ages 6–17 (134); a randomized, placebo-controlled trial of citalopram in children and adolescents ages 7–17 (135), a double-blind, randomized, placebo-controlled trial of escitalopram in children and adolescents ages 6–17 (136) which demonstrated significant improvement in adolescents only, and a follow-up trial of escitalopram in adolescents 12–17 (137). Only two SSRIs are currently approved by the FDA to treat pediatric depression: Fluoxetine is approved to treat depression in children eight years of age and older, and escitalopram is approved to treat depression in adolescents 12 years of age and older. Medications such as fluvoxamine have proven themselves safe and effective in treating other childhood disorders, i.e. obsessive-compulsive disorder. However, studies proving these medications safe and effective in childhood depression are lacking.

The SSRIs are metabolized in the liver by the cytochrome P450 isoenzyme system and differentially inhibit the cytochrome P450 isoenzymes, which can lead to drug-drug interactions with medications metabolized by the same isoenzyme (138). There is little information on the impact of age on absorption, metabolism, therapeutic levels, or possible drug interactions of SSRIs.

The AACAP guidelines recommend continued treatment with SSRI for 6–12 months after achieving an acceptable clinical response (139, 306). At this point, continuing antidepressant treatment as maintenance therapy may be required for patients with multiple or severe episodes of depression or patients at high risk for recurrence. Frequency of follow-up would be determined by factors such as stability of home environment, existence of comorbid conditions, and clinical status. Patients with recurrent episodes accompanied by psychosis, severe suicidality, or treatment resistance may even require lifelong treatment (139).

Common side effects for SSRIs include: gastrointestinal upset, decreased appetite, headache, restlessness, insomnia, and fatigue. These effects are usually dose-dependant and do not appear to be long-term (140). Recently concern about the use of SSRIs during pregnancy has been raised regarding the development of Persistent Pulmonary Hypertension of the Newborn (PPHN) in infants exposed to SSRIs late in pregnancy (141). Additionally, congenital malformations, particularly ventricular septal defects, may be linked to SSRIs, particularly paroxetine (142).

The possibility that SSRIs and antidepressant medication in general may increase suicide risk has also been raised. This concern surfaced after an FDA meta-analysis of 95 adverse event cases across 23 pediatric trials of antidepressants (140). While no individual trial demonstrated a statistically significant risk of suicidality, many trials had a relative risk of greater than or equal to two, increasing the concern of researchers. Suicidal behavior occurred most often in patients with a history of suicide attempts or ideation. In response to these concerns, the FDA has published a "black box" warning for all antidepressants, indicating a possible increased risk of suicidality in children and adolescents given antidepressant medications. The FDA has also requested all antidepressant medications be packaged in specific quantities. Patients should receive a medication guide with each prescription, alerting them to the increased risk of suicidal thinking and behavior (11).

The recent Treatment for Adolescents with Depression Study (TADS) addressed the concern of increased suicidality with SSRI medication for the treatment of depression in adolescents (143). In this study of 439 adolescents ages 12–17, the number of adolescents reporting suicidal ideation declined from 29% at baseline to 10.3% after 12 weeks. The treatment group receiving both treatment with fluoxetine and cognitive behavioral therapy proved to be statistically superior to placebo with respect to reducing reports of suicidal ideation. Recent toxicological and epidemiologic evidence also suggest a declining rate of suicide among children and adolescents, coinciding with increasing rates of antidepressant use in this population (140).

Another concern regarding the use of SSRIs in children and adolescents with major depression is the risk of "switching" to a manic episode. Recent literature suggests that children ages 10–14 on antidepressant medication are at highest risk for conversion to a manic episode (144), but further research suggests that children on SSRIs may be at lower risk for a manic switch compared to those on other antidepressants such as tricyclic antidepressants. However, further analysis of this data suggests pre-pubertal children (ages 5–14) are at higher risk of new-onset mania on SSRI treatment than older adolescents and adults (ages 15–29 years) (145). Other suggested risk factors for switching to a manic episode include family history of bipolar disorder and multigenerational mood disorders (140).

19.8.1.1.2. Tricyclic Antidepressants

Tricyclic antidepressants (TCAs), previously a mainstay of treatment for MDD, have been well studied and often utilized in adult patients. Studies of TCAs in adults with major depressive disorder have established their efficacy in acute (146) and maintenance treatment (147). Yet, literature reviews and a meta-analysis of 12 randomized controlled trials of TCAs in patients aged 6–18 years (148) have not supported efficacy in children and adolescents (149).

A literature search on the cardiovascular effects of TCAs in children and adolescents (150) found TCA use was associated with several cardiovascular events. Adverse reactions ranged from minor increases in systolic and diastolic blood pressures and heart rate to sudden death. Electrocardiographic changes were noted, but most were not age-related and were associated with higher serum-levels of medication. The American Association of Poison Control Centers Toxic Exposure Surveillance System reviewed all 168 cases of sudden death in children and adolescents in which there was a mention of the TCA desipramine, or four structurally similar TCAs, amitriptyline, imipramine, nortriptyline, and doxepin from 1983 to 2002 (151). The case fatality rate was significantly higher for children and adolescents on desipramine compared to all other TCAs. The authors recognize that the explanation for relatively higher rate of toxicity with desipramine compared to the other studied tricyclic antidepressants is largely unclear. They do, however, suggest that pharmacodynamic factors may be implicated (151).

19.8.1.1.3. Monoamine Oxidase Inhibitors

Historically, monoamine oxidase inhibitors (MAOIs) have been a second-line treatment for depression in adults (152) but they may be more effective than TCAs for depression with atypical features, i.e. increased sleep, increased eating, and weight gain (153). However, the dietary limitations and risk of tyramine-induced interactions have limited their use in children and adolescents (154).

To date, there are few studies of MAOIs in adolescents. In a chart review, Ryan et al. (155) assessed the efficacy of MAOIs in 23 depressed adolescents. Twenty-one of these subjects had not responded to heterocyclic antidepressants. Seventy percent of the adolescents reviewed in Ryan's study had a "good" or "fair" response to MAOIs alone or in combination with heterocyclic antidepressants. However, dietary noncompliance was a significant problem in 80% of the subjects. Because of the relatively high risk of noncompliance with a tyramine-free diet, the risks of MAOI treatment may outweigh the potential therapeutic benefits in unreliable adolescents or families (155). Newer MAOIs, such as moclobemide have benefits over the older, nonselective monoamine oxidase inhibitors. First, they do not appear to impair cognitive function in young adults as do older antidepressants (156). This is a significant advantage for school-age children. Second, these newer medications may not require the dietary restrictions of the older, nonselective inhibitors. Unfortunately, studies utilizing these medications in depressed children and adolescents are still lacking (152). In fact, no studies have been published testing any MAOIs in over two decades. In general, these agents tend to be used in responsible adolescents with treatment-resistant depression.

19.8.1.1.4. Other Antidepressants

Bupropion is thought to derive most of its antidepressant properties from its effect on the noradrenergic system and specifically its modulation of the reuptake of norepinephrine and dopamine in the CNS. Bupropion undergoes biotransformation to three pharmacologically-active metabolites. One in particular, hydroxybupropion, is associated with increased side effects, mainly dermatological and gastrointestinal (157). These side effects may worsen if bupropion is combined with other medications, such as fluoxetine. Concerns about seizures in adults with eating disorders have limited the use of bupropion. However, the incidence of seizures is low in adults when bupropion is given in limited doses. When the dose is under 450 mg/day in adults, seizures occur in approximately 4 per 1000 patients (158). With respect to pediatric data, several cases of presumed "serum-sickness" have been reported in patients on bupropion with a history of comorbid ADHD or bipolar disorder who subsequently developed depression (159). One controlled trial has been conducted in adolescents with depression and ADHD reported that sustained-release bupropion was associated with significant improvements over placebo in both depression and ADHD symptoms (160). Additionally, an open-label trial of sustained-release bupropion for adolescents with substance use disorders, ADHD and a mood disorder, found significant reductions in symptoms and functioning for all three disorders (161).

Venlafaxine inhibits reuptake of both serotonin and norepinephrine from the synaptic cleft. Like SSRIs, venlafaxine lacks significant affinity for muscarinic, cholinergic, histaminic, or α_1-adrenergic receptors (11). Venlafaxine is one of the few newer antidepressants to have pharmacokinetic data for children and adolescents (162). An initial double blind, placebo-controlled study of 33 children and adolescents aged 8–17 did not find improvement of depressive symptoms (163). The authors of this study suggest that cognitive behavioral therapy (CBT), which was administered to all subjects, may have masked the effects of venlafaxine versus placebo. A subsequent report described two randomized controlled trials in

169 children and adolescents with depression ages 7 to 17 years with venlafaxine ER for 8 weeks. Although neither study showed greater improvement in depressive symptoms than placebo, a post-hoc analysis revealed that the medication was superior to placebo among adolescents aged 12–17 but not among children aged 7–11 (164).

Trazodone and nefazodone have little published literature supporting their use in depressed children and adolescents. Trazodone derives most of its antidepressant properties from its action as a serotonin receptor antagonist (152). Two major side effects – priapism and sedation – have limited its use in children and adolescents. Nefazodone works at both sites of the serotonin (5-hydroxytryptamine [5-HT]) receptors. It blocks the 5-HT_2 receptor as a postsynaptic serotonin antagonist and inhibits presynaptic serotonin reuptake. In an 8-week open-label trial of nefazodone in 28 depressed children and adolescents (aged 7–17) nefazodone was generally well-tolerated (165). Nefazodone was also clinically effective for depressive symptomatology, although efficacy was not the major focus of the study. Nefazodone also carries an FDA black-box warning for hepatotoxicity. Therefore, patients on nefazodone should closely be monitored for this rare, yet severe event.

19.8.1.2. Electroconvulsive Therapy

Treatment with electroconvulsive therapy (ECT) may be considered in children and adolescents who do not adequately respond to multiple antidepressant medications and cognitive behavioral therapy, particularly if there is a family history of depression found only to be responsive to ECT (11). To use ECT in children and adolescents, two additional child and adolescent psychiatrists, in addition to the primary treating psychiatrist, need to agree that this level of treatment is indicated.

19.8.1.3. Transcranial Magnetic Stimulation

A few studies have begun to investigate repetitive trans-cranial magnetic stimulation (rTMS) for treatment-resistant depression in adolescents. This technique induces weak electric currents using a rapidly changing magnetic field. Over time, this intervention can change the excitability and inhibition of neural networks. Treatment effects are believed to reflect changes in synaptic plasticity akin to long-term potentiation and long-term depression (166). Two small pilot, open labeled studies have been conducted in treatment-resistant depression, which have both reported significant improvement in symptoms and good tolerability of the treatment. (167, 168). When these patients were re-assessed three months (168) and three years (169) later, the clinical improvements were maintained, and there was no evidence for long-term cognitive deterioration. These studies have prompted interest in further research investigating this treatment methodology using larger samples and controlled designs.

19.8.1.4. Bright Light Therapy

Bright light therapy (BLT) has been investigated as a treatment for depression symptoms in adolescents with both seasonal and non-seasonal depression. First, a placebo-controlled trial of light therapy for the treatment of pediatric seasonal affective disorder reported significant improvement in depression symptoms in the BLT group compared with placebo (170). In a later study, a randomized crossover trial was conducted using bright light therapy (BLT) as a mono-therapy for non-seasonal depression in 28 adolescents. This study found significant reductions in depression scores and elevation of evening melatonin levels to be associated with BLT (171). This group also examined BLT as an add-on therapy to fluoxetine and psychotherapy, and found a significant improvement in depression symptoms but no change in evening melatonin levels (172).

19.8.1.5. Vitamin D

Emerging research has examined the relationship between Vitamin D deficiency and depression. Vitamin D has components that overlap with the physiology of depression therefore affecting mood when the vitamin is low in the body. Vitamin D has been linked to sleep and circadian rhythms which, when disrupted, can exacerbate depressive symptoms (173). A recent meta-analysis of studies in adults confirmed an association in which depressed patients tend to have lower vitamin D levels, and that individuals with low vitamin D are at higher risk for depression (174). However, a recent case series in adults which also found lower vitamin D levels in adults with depression did not show improvement in depression symptoms as a result of vitamin D replacement (175). A Swedish study of 54 adolescents (ages 10–19) conducted in 2011 investigated the correlation between Vitamin D and well-being over the course of three months (176). Researchers found a significant decrease in depressive symptoms and an increase in well-being after taking a Vitamin D supplement. Controlled trials are needed to further assess whether Vitamin D assessment and treatment should be incorporated into routine care and treatment of adolescent depression.

19.8.1.6. Psychotherapeutic Treatment Options for Depression

The psychotherapeutic treatment options available for children with Major Depressive Disorder (MDD) and Persistent Depressive Disorder (PDD) are similar to those available to adults, but tailored to children. A biopsychosocial approach is the best for children and adolescents with MDD. This approach combines medication management, psychotherapy, social skills training, and educational assessment and planning (96). A combination of various short-term therapeutic techniques may be the most efficacious treatment option for the child or adolescent with a depressive disorder (177).

19.8.1.6.1. Cognitive Behavioral Therapy (CBT)

CBT is an effective treatment for depressed children and adolescents. It addresses the cognitive biases which maintain depression (11). CBT is based on the cognitive theory that individuals trigger and maintain depression by specific dysfunctional cognitive constructs (178). In CBT the child is the focus of treatment and has an active collaboration with the therapist to address the emotional processing of distressing issues and to develop coping strategies. Parents may be involved as "co-therapists" to reinforce the newly learned behaviors.

A study comparing 12–16 weeks of individual CBT, nondirective supportive psychotherapy, and systematic behavior family therapy in a group of 107 clinically referred, depressed adolescents found CBT was the most efficacious. CBT had the most rapid reduction in interviewer-rated and self-reported depression and the greatest increases in parent-rated treatment credibility (179). Wood et al. (180) studied the effectiveness of brief individual CBT and relaxation training for clinically depressed adolescent outpatients. A combination of cognitive, social problem solving, and symptom-focused interventions was associated with significant reductions in dysphoria and improved general adjustment. Patients who received CBT were more likely to remit from their depressive disorder than control patients.

As more studies are conducted on efficacy of CBT, its effectiveness for the prevention of depression in a high risk population (i.e. children of depressed parents) needs evaluation (181). A large multi-center controlled trial to assess the effect of CBT to prevent depression and anxiety in offspring of parents with depression and anxiety is currently underway (182).

19.8.1.6.2. Dialectical Behavioral Therapy (DBT)

Dialectic behavioral therapy (DBT) was developed out of cognitive behavioral therapy originally designed to treat symptoms associated with borderline personality disorder (BPD) in adults (183). There has been strong interest in adapting DBT for adolescents with depressive symptoms (184). A study of 12 adolescents tested the effectiveness of DBT on suicidal thoughts and depression over the course of one year (185). Researchers found a reduction in depressive symptoms and improved quality of life, which was associated with a reduction in self-injurious behavior and suicidal thoughts. Sunseri (2004) and Rathus and Miller (2004) also found positive effects including reduction in depression symptoms and self-injurious behaviors in suicidal adolescents (186, 187).

19.8.1.6.3. Family Therapy

Although there is only limited empirical research on its use, family therapy may provide helpful support for the depressed child or adolescent. Emphasis is on understanding a child's symptoms as they relate to the entire family unit (188). Observational studies suggest there is an association between the problems families encounter with a depressed child or adolescent and problems existing within the family. Such problems could include existing mental illness (other than the child's) in the family or strained relations due to the difficulties of interacting with a depressed child or adolescent (189). Research to explore the efficacy of other forms of family involvement for the treatment of adolescents and children with depression is being conducted. One such study conducted by Sanford et al. (2006) on family psychoeducation (FPE) found FPE influences processes which are thought to affect the course of adolescent depression (190). Its use increased parent-adolescent relationships and improved social functioning. FPE might have potential to reduce recurrence of subsequent major depressive episodes.

19.8.1.6.4. Attachment-Based Family Therapy

Attachment-based family therapy (AFBT) is a brief, manualized treatment for adolescent depression that focuses on repairing relationships between adolescents and parents, addressing attachment failures and rebuilding trust. Early evidence has suggested that this approach is effective in reducing depression symptoms including suicidal ideation in adolescents (191, 192). Recent work has suggested putative mechanisms underlying the benefits of this treatment. Increases in maternal autonomy-granting during ABFT was associated with improved perceptions of parental care and decreases in attachment-related

anxiety and avoidance. Decreases in adolescents' perceived parental control were associated with reductions in adolescents' depressive symptoms (193).

19.8.1.6.5. Group Therapy

Some consider group therapy the treatment of choice for adolescent depression because the developmental tasks of adolescence include emotional separation and individuation from parents and identification with a peer group (194). Fine et al. (195) compared two forms of short-term group therapy for depressed adolescents: a therapeutic support group (TSG) and a social skills group (SSG). Subjects in the TSG shared common problems, developed new ways to cope with stressful situations, and provided mutual support. Subjects in the TSG improved significantly more than those in the SSG. Adolescents treated in the TSG had significantly greater reductions in their depressive symptoms and increases in self-concept. However, these group differences were no longer evident at 9-month follow-up.

19.8.1.6.6. Psychodynamic Psychotherapy

Psychodynamic psychotherapy for adolescent depression emphasizes the importance of object loss and self-critical internal representations. Goals of therapy include a reduction in the use of maladaptive defense mechanisms, resolution of past psychological trauma, and greater acceptance of the realistic limitations of one's family and one's own abilities. The aim of psychodynamic psychotherapy is not only to relieve the symptoms of depression, but also to ensure maintenance of improvement and prevention of relapse through modification of the individual's adaptive style and personality organization (11).

19.8.1.6.7. Interpersonal Psychotherapy

Interpersonal Psychotherapy for Depressed Adolescents (IPT-A) is based on psychodynamic theory and it is derived from Interpersonal Psychotherapy originally developed for adult patients, but was modified for use in adolescents (196). IPT is focused on the current relationships of the patient. IPT is based on the principle that regardless of the underlying cause of the depression, the onset of symptoms occurs within an interpersonal context: depression can negatively impact interpersonal relationships, and problems in relationships can have negative effects on mood (197, 198). The goal of IPT is to improve relationships and develop better communication and interpersonal problem-solving skills (197, 198). IPT-A is delivered over the course of 12–16 weeks, which is divided into the initial phase, the middle phase and the termination phase. The initial phase includes explaining the theory and goals of IPT-A, identifying the interpersonal problem areas and developing a treatment plan with the patient (197, 198). The adolescent and therapist begin working on the conflicts during the middle phase. This includes communication analysis, decision analysis, and role playing (197, 198). During the termination phase, the therapist reviews the adolescent's depressive symptoms and changes that have occurred in communication and relationship skills, and discusses the management of future depressive recurrences (197, 198). Mufson and Fairbanks (199) conducted a study with depressed adolescents who each received 12 weeks of modified interpersonal psychotherapy in an open clinical trial then completed a follow up evaluation. Of 10 depressed adolescents who participated in the follow-up evaluation, only 1 met criteria for a mood disorder at the end of the trial. Most reported few depressive symptoms and had maintained improvement in social functioning, despite experiencing a significant number of negative life events. Improvements that occurred during the 12-week open clinical trial were maintained for the next year (199). A controlled trial was conducted in 63 adolescents and their families who were randomized to receive either IPT or treatment as usual delivered by school-based mental health clinicians (200). This study found that IPT was superior to treatment as usual for reducing depression symptoms. Furthermore, adolescents who reported higher levels of conflict with mothers and of social dysfunction with friends were particularly responsive to IPT as opposed to treatment as usual (201). Such findings have important implications for developing strategies for personalizing treatment based on individual characteristics.

19.8.1.7. Combined Treatments for Depression

Several large, controlled studies have now investigated whether a combination of treatments might be more helpful than single approaches for adolescents with MDD. All reports to date have examined adding CBT to a medication strategy.

The Treatment for Adolescents with Depression Study (TADS) was a 12-week, multisite, double-blind, placebo-controlled study of 493 adolescents (ages 12–17 years) with a diagnosis of major depressive disorder. There were four treatment groups: (a) fluoxetine only, (b) CBT only, (c) CBT plus fluoxetine, and (d) placebo. The combination treatment group had a 71% response rate, compared with 61% response rate for fluoxetine alone, 43% response rate for CBT alone, and 34.8% response for placebo. The combination of CBT and fluoxetine had a response rate twice that of placebo (122): a statistically significant difference. In addition, the combination of fluoxetine and CBT was superior to either fluoxetine alone ($P = .02$) or CBT alone ($P = .001$). After 12 weeks, the placebo condition ended but the active treatment groups continued open-label through 36 weeks.

The participants were then followed up naturalistically at one and five years following discontinuation of active treatment. At week 36, the estimated remission rates for intention-to-treat cases were 60% for the combination group, 55% for the fluoxetine group, and 64% for the cognitive-behavioral therapy group (202). One year following discontinuation of the TADS treatments, the benefit of all active treatment (week 36) persisted during followup on all measures of depression and suicidality (203). Almost half of the original sample was assessed for the five year follow-up. At that time, 96% of the participants had recovered from their index episode; of those almost half had a recurrence during the follow-up period (204).

The Treatment of Resistant Depression in Adolescents (TORDIA) was a 12-week, multisite, double-blind study of 334 adolescents (ages 12–18) with SSRI-resistant MDD (205). The adolescents were randomized into one of four treatment conditions: (a) switching to another SSRI, (b) switching to venlafaxine, (c) switching to another SSRI and adding CBT, or (d) switching to venlafaxine and adding CBT. Both combination treatment groups showed better responses than the medication-only groups. There were no clear advantages to either a second SSRI or venlafaxine, but venlafaxine was associated with greater side effects (increase in diastolic blood pressure and pulse, skin problems). The TORDIA results support the combination of using CBT and medication, however, the response rates for the combined treatment were 54.8% while just switching to either an SSRI or non-SSRI also yielded a fairly high response rate of 40.5%. This indicates a need for further research.

The Adolescent Depression and Antidepressant and Psychotherapy Trial (ADAPT) was a 12 week, multisite, pragmatic randomized controlled superiority trial of 208 adolescents ages 11–17 with moderate-to-severe MDD who did not respond to a brief initial intervention based on principles of routine clinical care for at least two sessions (206). Adolescents were randomized to start an SSRI or start a combination of an SSRI and CBT for 12 weeks. At week 12, 86 of the 208 (43%) adolescents reported being much or very much improved. In contrast to TADS and TORDIA, there was no significant difference in treatment effectiveness for the combined treatment (SSRI plus CBT) over just the SSRI alone (206). Predictors of a poor treatment response included baseline severity, obsessive-compulsive disorder and suicidal ideation, together with presence of at least one disappointing life event during the treatment (207). Predictors of suicide attempts during the treatment included baseline high suicidality, nonsuicidal self-injury, and poor family function. Predictors of nonsuicidal self-injury during the treatment included baseline nonsuicidal self-injury, hopelessness, anxiety disorder, and being younger and female (208).

19.8.1.8. Summary of Treatments for Depression

Recent practice parameters published by the American Academy of Child and Adolescent Psychiatry suggest starting with basic psychosocial interventions for youths with milder and/or simpler forms of illness, and recommending pharmacotherapy and/or specific therapy types (e.g. CBT or IPT) for those youths who do not respond to supportive psychotherapy or who have more complicated depressions (209). With regards to duration of pharmacotherapy, discontinuation could be considered six to twelve months after symptom resolution and medication should be gradually tapered (209, 210). These parameters noted that in order to prevent recurrence, some youths should be maintained with treatment for longer periods of time, and given the lack of research to date to guide clinicians in this area, clinicians are encouraged to trust their judgment and to consider individual factors such as clinical status, functioning, support systems, environmental stressors, and comorbidities (209).

19.8.2. Bipolar Disorder Treatment

In recent years, a substantial amount of progress has been made in testing interventions for youth with bipolar disorder, especially in regards to psychopharmacological interventions, and specifically for treating manic symptoms. Although previous guidelines had suggested that lithium or valproate should be used as first line agents for non-psychotic mania in pediatric bipolar patients (211), more recent review of the evidence has indicated that for youth, second-generation atypical antipsychotic medications have stronger evidence for effectiveness (212). Increasing evidence is available to suggest that pediatric bipolar disorder is a chronic illness and that children and adolescents frequently do not fully respond to a single intervention; rather, the majority of children will require multiple mood-stabilizing agents (213) and will benefit optimally from combined treatment with psychosocial individual and family interventions (214).

19.8.2.1. Pharmacotherapy

19.8.2.1.1. Lithium

Lithium was the first FDA-approved mood stabilizer for children and adolescents older than twelve years of age. Support for lithium in children and adolescents with bipolar disorder comes from several case reports (215). A large open trial (n = 100) suggested the benefit of lithium for treating acute mania in children and adolescents with bipolar disorder (216). However, a subsequent discontinuation study did not detect a significant superiority of lithium over placebo for preventing

relapse (217). In a small (n = 30) double-blind, placebo-controlled trial, Geller and colleagues reported that lithium was not significantly superior to placebo for treating mania in children and adolescents (218). More recently, Findling and colleagues published a report on 41 children and adolescents with bipolar disorder that had at least a partial response to an 8 week open-labeled trial of lithium and who continued long-term (mean 15 weeks) with lithium. This study reported that patients who initially responded to lithium maintained their response during the continuation phase, but that those who initially had a partial response did not improve during the continuation phase, even though adjunctive medications could be prescribed (219).

Lithium dosing is more complicated in children than in adults, as it is reported to have a shorter half-life and higher total clearance in children (220). The therapeutic range for lithium blood levels ranges from 0.6–1.2 mEq/L and is dependent on the individual's lithium excretion rate. Lithium levels should be monitored to avoid lithium toxicity. There are two major approaches to calculating a safe, effective dosage of lithium for children and adolescents with bipolar disorder: a weight-based method (215) and a kinetics-based method (221). The weight-based approach, applicable to 6 to 12-year-old children, recommends a dosage of 30 mg/kg/day in three divided doses and produces a therapeutic lithium level within 5 days (215). The kinetics-based model uses a single 600 mg lithium test dose to predict serum lithium levels in children (221).

Due to chronicity and unpredictability of symptoms in child and adolescent patients with bipolar disorder, the optimal duration of antimanic treatment is difficult to establish (11). However, evidence supports long-term maintenance therapy with lithium, as discontinuation of lithium has been associated with an increased risk of relapse (8, 222). Furthermore, restabilizing patients on lithium, once therapy has been discontinued or interrupted, can be difficult (223, 224).

Children treated with lithium should be carefully monitored for adverse effects on the renal and thyroid systems. Serum electrolyte levels should be obtained at regular intervals (225, 226). Some studies of lithium found an association with cognitive impairment, including confusion and forgetfulness, at even low lithium plasma levels (227). Other common lithium side effects in children, obtained from case reports, systematic reporting, and various efficacy studies, include weight gain, polydipsia, headache, tremor, acne, hypothyroidism, and GI complaints (nausea and diarrhea) (217). Renal, ocular, thyroid, neurological, dermatological, and cardiovascular side effects are less common (11). In addition, there has been concern regarding lithium therapy in sexually active adolescent females, as this medication has been associated with various congenital abnormalities, particularly Ebstein's anomaly, a malformation of the tricuspid valve.

19.8.2.1.2. Anticonvulsants

Anticonvulsant medications have been used in the acute and prophylactic treatment of bipolar disorder, particularly in the management of mixed states and rapid-cycling bipolar disorder.

Although valproate is commonly used in the acute treatment of children and adolescents with bipolar disorder, there is limited evidence to support its use. Valproate monotherapy had produced response rates of 53–80% in three open-label studies (228–230). However, a small (n = 15), double blind placebo-controlled trial failed to demonstrate effectiveness of valproate extended-release over placebo for children and adolescents aged 10–17 with bipolar disorder (231).

There are several safety concerns with valproate in children and adolescents; including hepatic failure, pancreatitis, and birth defects in the offspring of women on valproate therapy. Rare, yet potentially fatal hepatotoxicity appears to occur almost exclusively in children younger than two years of age and is more common among those on a combination of anticonvulsants (232). The North American Antiepileptic Drug Pregnancy Registry suggests a 10.7% rate of major congenital malformations (compared to a 2.9% rate in the general population), including neural tube defects and cardiac defects (pulmonary atresia) in the offspring of women who used valproate during pregnancy (233). Valproate has also been associated with hyperammonemic encephalopathy (particularly in patients with urea cycle disorders) (234), benign thrombocytopenia (235), and weight gain . Other side effects include sedation, nausea/vomiting, tremor, hyperglycemia, and alopecia (236).

Additionally, there has been concern of a possible valproate-induced metabolic syndrome, characterized by obesity, hyperinsulinemia, lipid abnormalities, polycystic ovaries, and hyperandrogenism, particularly in younger women exposed peripubertally. A proposed mechanism for development of this Polycystic Ovarian Syndrome (PCOS) in this population is that valproate-induced hyperinsulinemia leads to increased androgen levels and eventually PCOS. In a cohort of Finnish women taking valproate for seizures, 80% of those who began valproate before age 20 had polycystic ovaries or an elevated serum testosterone concentration, as compared to 27% of women taking other antiepileptics. Valproate has been associated with polycystic ovaries and elevated serum testosterone in women (237). Isojarvi et al. (1998) found the severity of this metabolic syndrome was reduced when valproate was replaced with lamotrigine in 16 women (suggesting a partial reversibility) (238). The generalizability of these findings to psychiatric populations is unclear as current reports are confined to women with epilepsy.

Carbamazepine is currently FDA-approved for the treatment of seizures in children and adolescents. Although double-blind, placebo-controlled studies in adults have shown efficacy for carbamazepine in acute mania (239), no controlled studied have shown carbamazepine to be effective as monotherapy in children and adolescents with bipolar disorder. In an open-label study that compared carbamazepine, valproate and lithium for children with bipolar disorder, both medications had similar effect

sizes [with valproate showing a non-significantly larger effect (228)]. In an open-labeled study of 27 children with bipolar mania treated with extended-release carbamazepine, Joshi and colleagues reported significant but modest improvement in manic symptoms, with failure to completely resolve manic symptoms at the end of the trial (240).

Many of the reports that support carbamazepine use in children and adolescents with bipolar disorder are in those with comorbid ADHD or conduct disorder (some of whom also had neurological disorders). Carbamazepine was effective in seven manic adolescents who did not response to lithium (241). It was a safe and effective treatment for acute mania and long-term maintenance treatment in three patients with juvenile-onset bipolar I disorder (242). However, other studies did not find carbamazepine more effective than placebo (228).

Carbamazepine is usually initiated at a low dose and is adjusted up based on tolerability to achieve blood levels ranging from 6–12 mcg/mL (242, 243). This typically corresponds to a maintenance dose of 10–20 mg/kg/day, given in divided doses, which could be as high as 1200 mg/day in adolescents (244, 245). Carbamazepine affects hepatic cytochrome P450, which results in carbamazepine inducing its own metabolism as well as that of other hepatically metabolized medications. This could result in lower than expected blood levels. Plasma levels should be checked after achieving a steady-state plasma concentration, particularly if carbamazepine is used with medications which utilize the cytochrome P450 system.

There is currently a black box warning for carbamazepine, as it has the potential to cause blood dyscrasias. Aplastic anemia, agranulocytosis (246) and leukopenia (247) have been reported with carbamazepine. Thus, complete blood cell counts with differential and reticulocyte counts should be monitored throughout carbamazepine therapy. Caution should also be used when prescribing carbamazepine to adolescent females, as relationships between carbamazepine and craniofacial defects, neural tube defects, and cardiac malformations have been reported (248). Other potential side effects include drowsiness, loss of coordination, vertigo, inappropriate antidiuretic hormone secretion, and cognitive/behavioral effects such as impaired performance in learning and memory tasks, irritability, agitation, insomnia, and emotional lability.

Oxcarbazepine, an analog of carbamazepine, has similar efficacy but has a lower risk of side effects. Thus, no blood level monitoring is required. As oxcarbazepine is a weaker inducer of Cytochrome P-450, it does not have as great an effect on drug-drug interactions as carbamazepine (249). Although case studies have supported oxcarbazepine use in bipolar disorder in children and adolescents (250, 251), a large, double blind placebo-controlled trial in 116 children and adolescents with bipolar disorder did not show that oxcarbazepine was superior to placebo for treating manic symptoms (252). Important adverse reactions reported with oxcarbazepine include drug-induced hyponatremia and dermatological/hypersensitivity reactions (253). In addition, oxcarbazepine may reduce contraceptive efficacy by altering plasma estrogen concentrations. Thus birth control options should be evaluated when treating bipolar females of child-bearing age (254).

Lamotrigine and topiramate are both approved for the treatment of epilepsy in adults and are used to treat children with atypical seizures. These medications are also currently being evaluated for use in bipolar disorder in children and adolescents. Several recent open-label trials found lamotrigine effective either as a monotherapy or as an adjunctive treatment (255–259). However, no results from controlled studies have yet been published for youth with bipolar. Further, an age-related association with Stevens-Johnson syndrome and other potentially-life threatening rashes (260) may limit its use in children and adolescents. Preliminary data of topiramate in bipolar youth found improvement of YMRS scores, but this was not statistically significant (261). The possibility of decreased sodium bicarbonate, leading to hyperchloremic metabolic acidosis in youths treated with topiramate for seizure disorder has been reported (262). Other possible adverse reactions from topiramate include impaired sweat production and cognitive impairment (263, 264).

19.8.2.1.3. Atypical Antipsychotics

Several case reports of children and adolescents who were unresponsive to other mood stabilizing medications found clozapine was effective in alleviating manic symptoms (265, 266). Furthermore, an open trial in hospitalized adolescents who had failed prior treatment on antimanic or other antipsychotic agents reported significant improvement in mood symptoms after several weeks of clozapine as either a monotherapy or as an adjunctive therapy. The most common side effects of clozapine were sedation and weight gain. Weekly blood draws are required when initiating treatment to monitor for clozapine-induced agranulocytosis, which hinders widespread use in children and adolescents.

Initial reports from case studies and chart reviews on the effects of olanzapine for children and adolescents with bipolar disorder were promising (267–269). Confirming this, a randomized controlled trial testing the efficacy of olanzapine to treat acute mania in 161 adolescents 13 to 17 years old showed response superior to placebo after one week and remission superior to placebo after 3 weeks (270). Olanzapine is now approved to treat bipolar manic and mixed episodes in adolescents aged 13–17. Common side effects of olanzapine are weight gain, somnolence, agitation and insomnia.

Risperidone has been well-established as an effective treatment for adults with bipolar disorder presenting with acute mania. An open-label study of twenty-two children and adolescents found a 70% response rate after eight weeks of treatment (271). A chart review of risperidone use in children and adolescents found an average weight gain of 1.2 kg per month, over

six months (272). A three week, double-blind controlled trial testing the efficacy of high-dose (3–6 mg/day) versus low-dose (0.5–2.5 mg/day) versus placebo in 169 children with bipolar disorder ages 10–17 years found significant clinical improvement in both treatment groups, and that the lower-dose group had a better side effect profile (273). A double-blind controlled trial comparing risperidone and valproate in 66 children and adolescents with bipolar disorder found that risperidone led to more rapid and greater reduction of both manic and depressive symptoms than valproate and that risperidone also had lower rates of adverse events and attrition than valproate (274). Risperidone is now FDA-approved for the treatment of bipolar disorder in children and adolescents aged 10–17.

A double-blind, placebo-controlled study of thirty hospitalized adolescents with either manic or mixed symptoms found quetiapine was as an effective adjunctive treatment when added to divalproex therapy (275). More recently, another double-blind placebo controlled study of 266 children and adolescents aged 10–17 years with bipolar disorder found that quetiapine dosed at both 400 mg/day and 600 mg per day was superior to placebo (276). Common side effects for quetiapine are somnolence, dizziness, dry mouth, elevated liver transaminases and constipation. Quetiapine is now FDA-approved as a mono-therapeutic agent and as an adjunctive agent for the treatment of bipolar disorder in children ages 10–17.

Several open-labeled trials have suggested that aripiprazole may be a safe and effective treatment option for pediatric bipolar disorder (277–279). A large, placebo-controlled trial in children and adolescents with bipolar disorder supported the efficacy of aripiprazole for the treatment of acute mania (280). Subsequently, a controlled study examining the long-term efficacy of aripiprazole as a maintenance treatment reported that after clinical stabilization with aripiprazole, children randomized to the placebo group (n = 30) experienced relapse significantly sooner than those randomized to maintenance treatment with aripiprazole (281). Aripiprazole is now FDA-approved both as an adjunctive treatment along with lithium or valproate and as a mono-therapeutic agent for the treatment of manic and mixed episodes in children and adolescents aged 10–17.

Two open-labeled trials have supported the possible efficacy and safety of ziprasidone for the treatment of bipolar disorder in children and adolescents (282, 283). A 4-week, placebo controlled trial conducted in 237 adolescents with bipolar disorder suggested that this medication was significantly more effective than placebo and well-tolerated. The results have not yet been published but are available on the FDA website (284). Ziprasidone is not currently FDA-approved for the treatment of bipolar disorder in children or adolescents.

All children and adolescents on atypical antipsychotics should be monitored for neuroleptic malignant syndrome, tardive dyskinesia, diabetes, and weight gain. They should also be alerted to the potential development of metabolic syndrome. In a comparative study, Ratzoni et al. (2002) treated fifty adolescents with risperidone ($n = 21$), olanzapine ($n = 21$), or haloperidol ($n = 8$). After twelve weeks, olanzapine was associated with the greatest relative average weight gain of 11.1%. The relative average weight gains on risperidone and haloperidol treatments were 6.6% and 1.5%, respectively (285).

Patients and their parents should be counseled about the risks and benefits of therapy before initiating treatment with an antipsychotic. Patients should also be encouraged to exercise and eat healthy food. In addition to monitoring their weight, fasting plasma glucose and lipid profile should be followed throughout therapy (286).

19.8.2.2. Electroconvulsive Therapy

Electroconvulsive therapy (ECT) has been an effective treatment for acute mania in adults (287). Studies in adolescents estimate a 75–100% response rate in mood disorders (288). However, ECT has been infrequently utilized, at least in part because of stigma associated with its use. Potential side effects of ECT include mild cognitive impairment, transient effects on short-term memory, anxiety reactions, disinhibitions, and altered seizure threshold (289). Current practice parameters suggest ECT be considered after a failure to respond to two or more trials of pharmacotherapy or when symptoms preclude waiting for a response to medication (288).

19.8.2.3. Treating Depression in Bipolar Children and Adolescents

While the vast majority of clinical research has focused on treating the manic symptoms of bipolar patients, treatment of children and adolescents with bipolar disorder also requires careful monitoring and treatment of depressive symptoms and episodes. Only a few prospective studies have directly addressed bipolar depression in youth. In an open-labeled trial of lithium monotherapy in 22 youth with bipolar depression, Patel and colleagues reported an effect size of 1.7 (290). In an open-label study, 46 youth with bipolar depression were treated with lamotrigine in combination with an atypical antipsychotic, and then given lamotrigine monotherapy in a 6 week maintenance phase. This study reported lamotrigine was well-tolerated and was associated with further reduction in depression symptoms (258). Another open-label study of lamotrigine monotherapy or adjunctive therapy for youth with bipolar depression found a large effect size for reducing depression symptoms (259). The only randomized, placebo-controlled trial that has been conducted in bipolar youth was a negative study. Quetiapine was not

found to be more effective than placebo for reducing depression symptoms in bipolar youth (291). The practice of using antidepressants to address depressive symptoms in bipolar patients has been controversial. Because antidepressants have been reported to elicit manic conversion, current guidelines suggest that adequate mood stabilization should be achieved before initiating antidepressant therapy (140).

19.8.2.4. Psychotherapeutic Treatment Options

Psychosocial treatments are a mainstay of therapy between acute episodes and are aimed at reducing morbidity and preventing relapse. A review of controlled trials conducted in adults suggested that psychotherapy treatments, when added to psychopharmacological interventions, reduce the risk of relapse of mood episodes and enhance social functioning (292). Although less work has been done with pediatric bipolar disorder, two randomized controlled trials have been conducted testing psychosocial interventions for youth with bipolar disorder. In a 2-year study, Milowitz and colleagues showed that as an adjunctive treatment to pharmacotherapy, patients that received family-focused therapy had better trajectories of depression symptoms in comparison to a psychoeducation control group (293). Another study showed that in addition to treatment as usual, a psychoeducation intervention was superior to wait-list control for improving mood symptoms for pediatric mood disorders (294). An additional factor to be considered in treatment is that bipolar disorder is often comorbid with other conditions such as disruptive behavior disorders, substance abuse, and learning disabilities. Each of these comorbid conditions will require specifically targeted psychotherapeutic interventions (295).

19.9. Summary

Mood disorders are major psychiatric disorders that occur at an increasing rate in children and adolescents. Historically, mood disorders have been undertreated and underrecognized in this population. Recent studies found that these disorders impact psychosocial functioning and impede developmental well-being. The high rates of comorbid anxiety disorders with major depressive and persistent depressive disorders make them more difficult to recognize and treat. Likewise, the similar presentation of ADHD and bipolar disorder hinders proper treatment. A careful assessment by clinicians and researchers will lead to earlier recognition and treatment. Continued research on the neurodevelopmental underpinnings of mood disorders in children and adolescents should provide the foundation for advancement in clinical practices.

In recent years, emerging evidence has begun to support validated evidence-based treatments for children and adolescents with mood disorders. For children and adolescents with depression treatment with SSRIs in combination with psychotherapy such as CBT, IPT, and group therapy adapted for use with younger patients are indicated (305). For children and adolescents with bipolar disorder, a range of psychopharmacologic options are now available, with increasing evidence supporting second-generation atypical antipsychotics as efficacious especially for pediatric mania (305). Emerging evidence suggests that family therapy may be useful in addition to mood-stabilizing agents. Research that focuses on developing empirically supported guidelines for psychosocial, pharmacological, and environmental therapy for children and adolescents with mood disorders is needed.

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20
Autism Spectrum Disorder

George M. Realmuto, M.D.

Abstract This chapter identifies the biological underpinnings, phenomenology, assessment and medical treatment of Autism Spectrum Disorder, a complex neurodevelopmental disorder. Basic science has made great strides in identifying the brain pathology of autism at various levels of scrutiny. This chapter reviews genetic, molecular, histological, anatomical and epidemiological levels of the disorder. Also, new assessment technologies have come on line to provide greater clarity in what collection of observations should be called autism and what would not. Although interventions that alter the newly identified pathophysiological processes are yet to be formulated, approaches to treatment that fail to take into account the current scientific evidence of the causes of autism can and should be avoided. The chapter describes an orientation to autism from the perspective of the scientific literature to provide a foundation for clinical decision-making for the practitioner.

Keywords Autism • Genetics • Histology • Neuroproteins • Assessment • Treatment

20.1. Introduction

How we evaluate, diagnose and treat autism is changing rapidly. Diagnostic and Statistical Manual 5 essentially eliminates autism as a discrete diagnostic entity and consistent with other neurodevelopmental disorders creates a continuum (1). Autism Spectrum Disorder (ASD) is one of twenty six diagnostic codes collected under the larger rubric of neurodevelopmental disorders in the American Psychiatric Association's newest diagnostic compendium. The diversity of disorders included span intellectual disability, Attention Deficit Hyperactivity Disorder as well as learning disorders and motor disorders including Tic disorders.

ASD can be plotted along a continuum of the essential ingredients of the original concept, now sixty years old, of Kanner's Autistic Disturbances of Affective Contact (2). Deficits of emotional reciprocity and nonverbal communication and the narrow interests of the individual with autism remain. The distinction for DSM-5 from its predecessor is the constriction of the richness of the menu of criteria.

Left as historical footnotes are the archaic views of causes now replaced by rich and exciting scientific data. This growing body of empirical research quickly moves the frontier of our understanding of the disorder and re-defines the medical basis of ASD. This chapter discusses some of the newer studies that have implications for our medical approach to the syndrome. Going forward, new research will need to validate whether findings from studies of a *forme fruste* or lesser variants are equally relevant to its most severe form. Studies with subjects that are more compliant because they are on the higher end of the spectrum and can participate may produce data that can generalize to the entire spectrum. Research however, on brain tissue collected under previous diagnostic taxonomies may not be valid to the entire range represented by ASD.

One gets a sense from recent provocative findings in genetics, immunology and neurochemistry that the field is much further along towards a comprehensive view of etiologies and that bridges built between these different paths of inquiry will change medical practice. For example, the American Academy of Child and Adolescent Psychiatry's newest practice param-

G.M. Realmuto, M.D. (✉)
Professor, Department of Psychiatry, University of Minnesota School of Medicine, Minneapolis, MN, USA
e-mail: realm001@umn.edu

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eters recommends testing for genetic abnormalities in individuals with ASD that was not a specific recommendation in the past (3). Recommended testing includes: Banded karyotype, Fragile X testing or chromosomal microarray (CMA) testing. Positive yield from CMA testing is as high as twenty-four percent (4).

The direction of this chapter proceeds from diagnostic identification to treatment covering the areas of epidemiology, genetics, comorbid disorders, brain findings, and both biological and educational/psychosocial interventions. The perspective is clinical practice but the background may stray to advances that have implications in the near future. The information may permit rational clinical decision making to best direct care and inform caregivers of the many aspects of causes and treatments for the affected individuals.

20.2. Diagnostic Criteria, Assessment and Measures

Variation in the quality and quantity of information applied to diagnostic algorithms can lead to low inter-rater reliability and diagnostic disagreements among practitioners. Therefore obtaining sufficient and specific information and firmly establishing the criteria upon which a diagnosis is based can be crucial in improving diagnostic accuracy. The latest version of the DSM was meant to better align with the International Statistical Manual of Mental Disorders 10th revision. As noted above, DSM-5 truncates the items from its predecessor while maintaining fidelity to the overarching concept of autism. This change prompted parents and advocates to project fewer individuals eligible for the diagnosis. Specifically individuals formally diagnosed as Asperger's disorder (AD) would no longer qualify for a diagnosis of ASD. Consequences could then include loss of disability benefits including educational and behavioral supports at home and school. Qualifying high functioning individuals, who previously were diagnosed with AD, with an ASD diagnosis would require fulfilling three criteria from the section on social communication and interaction as well as two criteria from the section on repetitive behavior, interests or activities. This may be a challenge if the most serious and prominent difficulties are social communication. Symptoms such as lining up toys or indifference to pain/temperature or the need to eat the same food every day may not apply to individuals previously diagnosed as AD. This may have more implications for new cases as the DSM text clearly says that "individuals with a well-established DSM-IV diagnosis of AD should be given the diagnosis of autism spectrum disorder". The alternative for cases of AD that no longer fit ASD criteria is to recognize social communication as the most prominent aspect of dysfunction for which the manual recommends consideration of the category social communication disorder. Another important change is the downgrading from major to minor the prominent, difficult to manage and environment impinging sensory dysregulation of autism. In the new diagnostic criteria sensory dysregulation is but one of four symptom classes within the second major symptom block of restricted and repetitive patterns of behavior.

A new aspect of a diagnostic evaluation for ASD is the application of severity and specificity modifiers to more fully describe the clinical presentation. Severity is tiered to three levels. Level one severity identifies an individual who requires some support to function in a variety of settings. The other two levels are linked to even higher levels of social deficit and inflexible behavior. Level two 'severity' matches with marked deficits and level three with severe deficits. An example of level three severity coincides with needs for support necessary to manage behaviors arising from transition from one school activity to another that caused great distress perhaps leading to aggressive behavior. Level three severity would thus be appropriate for this level of behavioral dysfunction. Severity may also be rated for the two major symptom domains. Social communication could be rated from one to three levels of severity and restricted range of behaviors at another severity level independent of the social communication rating.

The other modifier is specifiers. There are five possible specifiers: 1) ASD accompanied by intellectual impairment, 2) ASD accompanied by language impairment, 3) ASD associated with a known medical or genetic condition or environmental factor, 4) ASD associated with another neurodevelopmental, mental or behavioral disorder and 5) ASD associated with catatonia. Dexterity with the five types of specifiers is now a part of a complete medical diagnosis. For specifier two, how descriptive should the accompanying statement be? It might include: "fair receptive language and very poor expressive communication with the capacity for only short phrases. Specifier 4 could include the presence of Attention Deficit Hyperactivity Disorder (ADHD) combined and generalized anxiety disorder. Specifier five requires the use of its own DSM code for catatonia which is 293.89.

The consequences of adding the severity and specifier modifiers can border on the unwieldy. For example the diagnosis may look like: ASD accompanied by moderate intellectual disability with accompanying severe expressive language impairment and moderate receptive language impairment with very limited vocabulary with even greater limitations of communicative intent, with a genetic abnormality at 22q11.2 similar to velocardiofacial Disorder, with delivery at 28 weeks accompanied by anoxia without catatonia with level two severity of language and level 3 severity of restricted, repetitive

behavior due to inability to tolerate routine transitions without extreme aggressive behavior. Further, the extent of the work required to obtain the information to quantify and describe all of these qualifiers is extensive and may be prohibitive in many community clinics as currently resourced.

Previously associated as a member of the Pervasive Developmental Disorders in DSM-IV was Rett's syndrome. The association of Rett's syndrome and ASD is dealt with differently in DSM-5. Rett's syndrome would be listed as ASD with a description of a known genetic disorder. Under specifier number three the condition would be ASD with Rett's syndrome. Rett's syndrome is a known genetic disorder where early phenotypic presentation overlaps that of ASD. Heller's Syndrome (6) a forerunner of Child Disintegrative Disorder (7), a very rare condition and now attributable to Lipid storage diseases or Subacute Sclerosing Panencephalitis no longer inhabits the ASD category.

Another aspect of the newest diagnostic criteria may include changes in prevalence. This will be discussed in the section on epidemiology below.

The 10th revision of International Statistical Classification of Diseases (ICD-10) (5) includes Childhood Autism, Atypical Autism, Rett's Syndrome, Other Childhood Disintegrative Disorder, Overactive Disorder associated with Mental Retardation and Stereotyped Movements, AD, Other Pervasive Developmental Disorders and Pervasive Developmental Disorder, Unspecified. Therefore with the exceptions for Rett's syndrome, Childhood Disintegrative Disorder, Overactive Disorder associated with Mental Retardation and Stereotyped Movements, the other conditions will fall on the ASD spectrum (Table 20.1).

Sources of diagnostic information including direct observation of the patient in multiple settings and an accurate developmental and current history from multiple sources are the foundation of an accurate diagnosis (8). Instruments have been developed to improve diagnosis by assisting the practitioner in collecting information necessary to fulfill criteria. Some of the instruments include practitioner delivered diagnostic interviews. Others are self-administered checklists for parents/guardians or other knowledgeable informants that solicit developmental and psychopathological information. Diagnostic reliability improves when multiple methods of data collection are combined (9).

About a half dozen diagnostic instruments are available for systematic diagnostic data collection. They are age specific, parent rated or interactive and clinician rated. Among the various diagnostic instruments and structured interviews for

TABLE 20.1 ICD-10 criteria for childhood autism.

Childhood Autism

A. Abnormal or impaired development is evident before the age of 3 years in at least one of the following areas:
1. receptive or expressive language as used in social communication ;
2. the development of selective social attachments or of reciprocal social interaction;
3. functional or symbolic play;

B. A total of at least six symptoms from 1), 2) and 3) must be present, with at least two from 1) and at least one from each 2) and 3):

1) Qualitative abnormalities in reciprocal social interaction are manifest in at least two of the following areas:
- a. failure adequately to use eye-to-eye gaze, facial expression, body posture, and gesture to regulate social interaction;
- b. failure to develop (in a manner appropriate to mental age, and despite ample opportunities) peer relationships that involve a mutual sharing of interests, activities, and emotions;
- c. lack of socioemotional reciprocity as shown by an impaired or deviant response to other people's emotions; or lack of modulation of behavior according to social context; or a weak integration of social, emotional, and communicative behaviors;
- d. lack of spontaneous seeking to share enjoyment, interests, or achievements with other people (e.g. a lack of showing, bringing or pointing out to other people objects of interest to the individual).

2) Qualitative abnormalities in communication are manifest in at least one of the following areas:
- a. a delay in, or total lack of, development of spoken language that is not accompanied by an attempt to compensate through the use of gesture or mime as an alternative mode of communication (often preceded by a lack of communicative babbling);
- b. relative failure to initiate or sustain conversational interchange (at whatever level of language skills is present, in which there is reciprocal responsiveness to the communications of the other person);
- c. stereotyped and repetitive use of language or idiosyncratic use of words or phrases;
- d. lack of varied spontaneous make-believe or (when young) social imitative play.

3) Restricted, repetitive, and stereotyped patterns of behavior, interests, and activities are manifest in at least one of the following areas:
- a. an encompassing preoccupation with one or more stereotyped and restricted patterns of interest that are abnormal in content or focus; or one or more interests that are abnormal in their intensity and circumscribed nature though not in their content or focus;
- b. apparently compulsive adherence to specific, nonfunctional routines or rituals;
- c. stereotyped and repetitive motor mannerisms that involve either hand or finger flapping or twisting, or complex whole body movements;
- d. preoccupations with part-objects or nonfunctional elements of play materials (such as their odor, the feel of their surface, or the noise or vibration that they generate).

C. The clinical picture is not attributable to the other varieties of pervasive development disorder: specific developmental disorder of receptive language with secondary socioemotional problems; reactive attachment disorder or disinhibited attachment disorder, mental retardation with some associated emotional or behavioral disorder; schizophrenia of unusually early onset; and Rett's syndrome.

children with ASD is the Autism Diagnostic Interview-Revised (ADI-R.). This is a semi-structured interview with caregivers of children as young as 18 months who have ASD features (10). The ADI-R is particularly effective in differentiating children with autism from patients with mental retardation and language impairment (11). Another instrument, the standard research method for establishing a diagnosis, has made its way into the clinic. The Autism Diagnostic Observation Schedule (ADOS) is a semi-structured interactive instrument that can be administered to individuals suspected of autism spectrum disorder. Delivery of the stimuli to the child and rating of response requires a thorough understanding of normal development. To be used effectively and with diagnostic precision, practitioners must be trained to specific observable child criterion. Delivery consists of presenting stimuli to which the child responds or "presses" from which the patient's social, language and motor responses are evaluated. The measure consists of four, thirty-minute modules, designed to accommodate the expressive language abilities of the child to be tested (12). The ADOS is not suitable for adolescents with severe or profound mental retardation (13). An older instrument that can assist with diagnostic evaluation is the Autism Behavior Checklist (ABC). This 57-item instrument has shown promise in screening children for the autistic disorder although changes in diagnostic criteria over time and a decrease in emphasis on sensory characteristics limit its current applicability (14–16). The Childhood Autism Rating Scale (CARS) is another older instrument that is valuable for screening. The instrument organizes the practitioner's interactions with the patient and rates the child's response which is then compared to norms for average developing children, children with mental retardation, and children with ASD, along thresholds of several subscales. Convergent validity studies have been conducted with findings of high agreement between DSM-IV and CARS (17). Finally, newer instruments, the Gilliam Autism Rating Scale (18) and the Parent Interview for Autism (20) and the Social Responsiveness Scale (19) are parent rated instruments that have been found to be helpful and are becoming widely disseminated for screening and diagnostic purposes.

As these instruments were developed with clinical conceptualizations and diagnostic criteria that are now dated, newer instruments or analysis of their discriminative properties for DSM 5 must be taken into consideration.

20.2.1. Assessment Instruments

Beyond diagnostic assessment, there are other domains of functioning such as communication, intellectual capacity, special sensory and neurological status as well as consideration of a genetic evaluation that need to be assessed as part of a core evaluation. Furthermore, as cognitive functioning is an accurate predictor of outcome and can guide educational planning and its dysfunction is a common comorbid feature of autism, its evaluation should be part of an initial assessment. The Leiter International Performance Scales-Revised is useful especially when language skills are very deficient (21).

Language functioning, one of the main features of the disorder, should also be assessed also with an eye towards prognosis and planning for the future. Pragmatic language i.e. communication in the context of a social interaction, should be assessed as this is the area of speech that more clearly distinguishes children with autism from conditions that also have language related problems. The Children's Communication Checklist (22) is one instrument that may be suitable for this purpose.

Finally, level of adaptive ability may round out the initial evaluation. In cases where intellectual functioning is below average, subaverage adaptive functioning is the additional component necessary for a diagnosis of Intellectual Deficiency. The Vineland Adaptive Behavior Scales is the mainstay of this kind of assessment (23).

As will be clearer following the section on genetics and comorbid disorders, assessment for newly diagnosed cases should include DNA testing for fragile X and Williams and Angelman syndromes with fluorescent in situ hybridization testing (FISH). Testing to rule out metabolic disorders as part of a differential diagnostic evaluation involves analysis of urine or blood for histidinemia, and measures of important metabolic enzymes such as phosphoribosylpyrophosphate synthetase, dihydropyrimidine dehydrogenase, adenylosuccinate lyase, and 5'-nucleotidase. Another laboratory measure to be considered in cases where there is a history of pica, is a lead level. The consequences of early lead intoxication on CNS development are well known. Finally, one of the cardinal features of autism is language delay and in the context of poor language development a test of hearing such as auditory brainstem evoked response in very young children or audiometric examination in older children should be considered.

20.3. Genetics

The evidence that Autism is highly hereditable is persuasive. A sibling's risk for a diagnosis of autism in a sibship with autism is estimated to be 45 times that found in the general population (24). When twin studies are considered, the genetic component to the disorder is further reinforced. The rate of autism in dizygotic twins has been reported to be as high as 24%, but the rate for monozygotic twins is much higher, as high as 91% in some studies (25–27). While heritability estimates

suggest autism is one of the most heritable of the psychiatric disorders this is not to imply that it arises from a single locus. Several studies have considered as many as 10 to 20 loci to be involved in its expression (28). Analysis of family genetic studies estimate up to 10 interacting genes contribute to susceptibility to autism (29). The genetic abnormalities involved with other portions of the ASD spectrum are less clear. There may be considerable overlap of genetic abnormalities among all portions of the spectrum. However, it could be hypothesized that specific genetic aberrations are better makers for what was DSM-IV autism than for the ASD. Genetic studies that seek to determine the etiological and prognostic significance of genes associated with ASD will need to be clear about defining what portion/severity/specifier of the spectrum is being evaluated.

The pursuit of specific susceptibility genes for autism has a long history of promise but has been beset with obstacles and disappointment. Consensus is lacking between studies, but this is also typical of genetic research in psychiatry and research with polygenic disorders. Autism might best be thought of as exemplifying a disorder of genetic heterogeneity where vulnerability conveyed by particular alleles may be common in the general population. Susceptibility genes have included loci on 2q, 7q and 13q chromosomes (30–32). A recent genome wide screen of multiplex autistic families showed a number of chromosomal regions with LOD scores>= to 1.5 although none reached statistical significance. Loci included 3p25.3, 6q23.2, 12p12.1, 16p12.3, 16p13.2, 17q11.2, 17q21.2, and 19p13.11. Of these 17q and 19p received the most support (33). The 19p locus appears to be associated with the timing of a number of motoric, language and functional milestones. Other genome wide screens have also lent some support for these loci (34–36). McCauley et al. (33) also identified the 17q11.2 locus. This site is a popular candidate locus in psychiatric disorders and purportedly, may contain a gene for coding of the serotonin transporter protein (33). Another recent genome screen has also implicated this site (31).

Progress in the discovery of genes associated with ASD include the link of Rett's syndrome to a mutation at the MECP2 locus on the X chromosome and the proliferation of the mGluR5 receptor and FMR1 gene expansion of the CGG trinucleotide repeat (37, 42).

Rather than approach autism as a genetically homogenous disorder, a research strategy that considers each domain of the disorder as its own source of genetic variability might prove useful in identifying putative genetic loci. Language impairment for example is one of the hallmarks of the disorder. Research with impaired language individuals has generated empirical evidence for specific susceptibility loci. In one study, the language profiles of children with autism have been shown to have deficits similar to that of children with Specific Language Impairment (38). A recent study showed that loci implicated in specific language impairment overlapped with loci from an autism sample. Sites on chromosomes 13q21 and 7q31 for both conditions were identified (39). This approach appears to confirm the relevance of using candidate genes from disorders with related dysfunction as potential sites for investigation of similar phenotypic expression in autism. Another approach is to identify endophenotypes (40) and seek genetic linkages to these underlying biological foundations of the disorder. Possible choices might be phrase speech delay, seizure disorder, hyperserotonemia, poor eye contact and facial recognition, reciprocal gaze, or some other associated phenomenon that is not contained in the definition of the disorder, is in some way an intermediate phenotype and is likely to have a set of genes that code for its expression. The delay in the acquisition of phrase speech which may be governed by the 7q31 locus is an example of an endophenotype with a putative genetic locus.

20.4. Comorbid Medical Disorders and Autism

The prevalence of various comorbid medical and neurodevelopmental conditions in autism is around 10% but with a much higher rate if associated with profound cognitive delays (41). While this rate of comorbidity may appear high, it is still lower than, for example, the psychiatric comorbidity rate for ADHD. More interesting perhaps is the increased rate of other neurodevelopmental disorders comorbid with ASD. This being the case, the possible common genetic links between the group of neurodevelopmental disorders seem intriguing and worthy of exploration. Alternative hypotheses to a genetic association could include the similarity of behaviors expressed as a consequence of the mismatch between the requirements of an environment exposure and inherent individual ability. Of the disorders with some phenotypic overlap with ASD and known genetic association are Angelman, Fragile X (42) and tuberous sclerosis (TS) (43). Because specific genetic loci have been associated with this subgroup of neurodevelopmental disorders their association with autism speaks to the possibility of overlapping chromosomal loci. Prader-Willi and Angelman syndromes have known chromosomal abnormalities at 15q11-q13. That site may be important for understanding how comorbid neurodevelopmental disorders may share a common genetic vulnerability with ASD (44, 45).

Fragile X Syndrome is the most common form of mental retardation affecting about 1 in 4,000 males and 1 in 8,000 females (46, 47). Fragile X is caused by an instability of a portion of the X chromosome due to an expansion of a three nucleotide repeat of CGG sequence. Approximately 15–25% of cases of Fragile X syndrome also have autistic disorder (48, 49).

Conversely the prevalence of Autism with Fragile X syndrome is only 2–5% (50–52). Assessment for the Fragile X gene expansion in a group of individuals with autism will turn up a small number, but results will have implications for reproductive decisions and genetic counseling for relatives.

Tuberous Sclerosis (TS) is a disorder in which 25–60% of affected individuals have significant autistic traits. TS is an autosomal dominant disorder characterized by the classic triad of mental retardation, epilepsy and skin lesions (53). The co-occurrence of autism spectrum disorder and TS has been recognized for decades. The prevalence of the TS triad in ASD individuals is estimated to be about 1–4% (54). The features of autism spectrum disorder are present in 20 to 25% of the individuals with tuberous sclerosis (55, 56). The genetic characteristics of TS is quite interesting in that a similar phenotype is expressed by two separate genes each of which contributes to about half of the cases. One of the sites is found on chromosome 16 and one on chromosome 9 (55). Awareness of the relationship between these two disorders is important to consider during the assessment of individuals with either disorder. The incidence of Down's syndrome in children with autism is estimated to be as high as 11% (57, 58). Down syndrome is caused by three copies of chromosome 21, (trisomy 21), or the less common cause of Down's syndrome, the translocation of a part of chromosome 21 to another chromosome. Because of the prominent physical features and expected delays, associated ASD comorbidity may be overlooked leading to a delay in making the ASD diagnosis (59).

People with autism have more than a 100 fold increased risk of developing neurofibromatosis 1 as compared to the general population (60, 61). Also known as von Recklinghausen's Neurofibromatosis, it is identifiable by multiple cafe-au-lait spots and neurofibromas on or under the skin. The neurofibroma tumors may also develop in other ectodermal tissues including the brain. About 50% of people with NF1 also have learning disabilities. There are multiple reports linking the neurofibromatosis 1 (NF1) gene and autism (62, 60).

A less well-known disorder that can present with ASD includes Smith-Magenis syndrome. Some of the physical characteristics of this disorder include low muscle tone and feeding problems in infancy, short stature, flat facial features, prominent jaw in older children and adults, downturned mouth, short fingers and toes, heart defects and murmurs. In most cases the affected individual is socially connected but some cases also present behavioral components associated with ASD. The genetic etiology of this syndrome is an interstitial microdeletion at chromosome 17p11.2 (63). Prader-Willi, Angelman, Fragile X, tuberous sclerosis and Down's syndrome may provide a clue to the multifocal genetic sites that may contribute to the ASD phenotype. In addition to the implications for the pursuit of gene loci in ASD there are implications for diagnosis and intervention. Vigilance during the initial workup for these disorders will expand the clinician's differential diagnostic perspective. Clinicians serving the developmentally disabled should be alert for ASD comorbidity. For the clinician serving patients with ASD, a referral for genetic testing should be considered when a patient with ASD has dysmorphic features or unusual physical and developmental trajectories that are not typical for ASD.

20.4.1. Special Sensory Disorders and Autism

The presence of ASD in congenitally blind children is interesting for its environmental and sensory developmental implications for causation. The features of autism including social deficits, stereotypies and narrow range of interests are strikingly common in some cases of congenital blindness (64–67). Special services that augment social input through alternative sensory modalities and preventing sensory deprivation and social isolation are important treatment goals.

Co-occurring deafness and ASD is well documented in the literature (68–71). One study to consider this association looked at the auditory capacities of a group of 199 children and adolescents with autism; mild to moderate hearing loss was present in 7.9% of these children (68). Profound deafness presents challenges for diagnoses of profound social and communication disorders. The clinician will be faced with difficult questions: Does the deafness explain the social and communication deficits? Are these features better attributed to a pervasive developmental disorder, namely ASD?

20.5. Neuroimaging Findings

ASD is a neurodevelopmental disorder affecting the outflow of the central nervous system (CNS). Evidence for CNS disturbances should be found in differences in imaged brain structures or imaged brain activity or imaged brain metabolic processes between affected and unaffected individuals. There are many studies that have pursued this direction. One of the most replicated neuroanatomical findings is large brain volumes in individuals with autism. This phenomenon has been refined in several studies to reveal a pattern of increases in cerebral white and gray matter volume in early childhood compared to unaffected children and a reversal in adolescence leading to smaller volumes (72–75). Abnormally reduced volume in specific cerebellar sites has also been reported (76). The picture for a neuroanatomical signature for the disorder has hardly emerged

however. Evidence for similar neuroanatomical cerebral volumes, i.e. decreased cerebral white matter volumes, between monozygotic twins discordant for the older narrowly defined disorder of autism, suggests simple anatomical differences being too limiting as a research paradigm. Additional hypotheses in conjunction with neuroanatomical findings that support a spectrum of phenotypic expression are necessary (77). Other neuroanatomical findings that are relevant in understanding the disorder include poor connectivity at the temporoparietal junction (78). Decreased grey matter volume in the right paracingulate sulcus, the left occipito-temporal cortex and the left inferior frontal sulcus were found in a well-controlled MRI study. Also found was increased volume in the left amygdala/peri-amygdaloid cortex, the right inferior temporal gyrus and the left middle temporal gyrus. The common thread to these areas could be the amygdala and its role in connecting emotional stimuli through various other higher-level brain areas (79).

Other methods for defining neuroanatomical differences rely on tests that provoke specific brain activity and create images of the substrates that support that function. For example, a task involving evaluation of social perspective, (Theory of Mind) was administered to high functioning individuals with ASD. The task required the participant to make choices based on the ability of the subject to appreciate the emotional and cognitive position of others while brain activity was imaged with Positron Emission Tomography. The area of the brain that was active for controls, the anterior cingulate and the medial frontal cortex, was less active in the affected group (80). These findings may tell us about the higher level processing required for sophisticated social functioning. Increasing the activity in these social brain areas as a treatment strategy or looking for specific genetic and/or neurochemical differences that support these functions in areas of the brain that regulate these frontal structures are possible research directions.

20.6. Histopathology

The previous section outlined imaging procedures that have been useful in elucidating both the sources of and the relationship between symptomatic dysfunction and anatomical correlates in ASD. A finer grained approach to the disorder brings histopathological procedures that are able to reveal pathology at the level of the individual neuron. The overall picture from these studies has suggested that the limbic system and the cerebellum are abnormally structured (81–83, 202). One of the earliest histological abnormalities identified reduced numbers of Purkinje cells in the cerebellum. These large cells were found to be decreased in number or atrophic (82, 84). The areas most affected are the posterolateral neocerebellar cortex and adjacent archicerebellar cortex of the cerebellar hemispheres (85). Other areas of the brain were also shown to have abnormalities in neuronal configuration, size or density. The hippocampus, subiculum, entorhinal cortex, amygdala, mammillary body and medial septal nucleus and the anterior cingulate gyrus showed reduced cell size and increased cell density (82). Because many of the structures on this list are parts of the limbic system, a possible brain/social behavior association could be considered. Limbic structures are important in emotional processing. The identification of limbic histopathology could be linked to the social deficits that are a hallmark of ASD.

Bauman and Kemper's early histological postmortem work is the foundation for the field's understanding of the medical basis of autism (86). Their detailed findings noted specific abnormalities in the limbic system and the cerebellum (82). Special staining of the pyramidal neurons in the hippocampus showed decreased complexity and extent of dendritic arbors in this region (87). Other investigators building on this work found increased neuronal density and irregular laminar patterns, increased number of neurons in layer 1 of the cortex and abnormally oriented pyramidal cells (88). Additional evidence for neuronal abnormalities comes from Casanova, (89), who found increased numbers of cortical minicolumns which were smaller and more compact in subjects with autism than in controls. Systematic histopathological examination by Bauman and Kemper, (90–92), has continued to add to our knowledge of the neuropathology in autism. Their painstaking work when extended to the cerebral cortex showed small neuronal cell size and increased cell packing density in the anterior cingulate gyrus. Having made these noteworthy discoveries they considered neurodevelopmental aspects of the pathological process. Changing patterns of neuropathology from childhood to adulthood is reported. For example, they found that neurons in the nucleus of the diagonal band of Broca were unusually large but of adequate numbers in children less than 13 years of age. When autistic brains older than 21 years of age were examined a decreased number of small pale cells were found (91). This could suggest an ongoing rather than a single strike pathophysiological process. Another example of developmental changes that could suggest a continuing neuropathologic process are the differences found in the cerebellum in the fastigial, globose and emboliform nuclei in the roof of the cerebellum. In the brains of children under 13 that were examined, the neurons were found to be enlarged and in adequate numbers. However, in adult brains the neurons are small, pale and decreased in number (82). Finally, in keeping with a possible persistent process of ongoing abnormalities are changes in brainstem neurons. In the inferior olive of the brainstem, neurons of individuals with autism show a decrease in size over time. It is known that efferent fibers from the olivary nucleus terminate on Purkinje cell dendrites. Loss of Purkinje cells would likely lead to retrograde loss of the olivary neurons but as noted they remain although diminished in size. Retrograde atrophy can only be a factor if

the connection between the two neuron groups was previously established. The connection is believed to occur early in pregnancy. Thus, the connection between Purkinje and olivary neurons was not established leading to the preservation of the olivary neurons. This connection is solidified after about 28–30 weeks of gestation. The findings reported could only have occurred secondary to a genetic, environmental or other neurodevelopmental insult occurring before the fetus reaches 28 to 30 weeks of age (93). Histological changes that have their impact early in neonatal life as well as changes that appear to be ongoing through development defy a known neuropathological disorder. Illumination of a genetic, environmental, infectious or other etiologic process awaits further study (93).

20.6.1. Immunohistology and Molecular Studies

Immunohistochemical studies use procedures that identify and localize specific proteins often by devising antibodies that tag the target antigen. An investigation of the density of a group of trophic neuroproteins around which the brain organizes the position and viability of neurons may hold explanatory relevance to explain known brain histopathological abnormalities in autism. Support for trophic factors being important causes of cytoarchitectural abnormalities can be found in the work of Casanova (89) and Bailey (88). In addition, differences in these substances in the brains of autistic individuals compared to controls may support brain/behavior correlations. Fatemi et al., in 2001, examined the quantity of an anti-apoptotic protein Bcl-2 in an area that had been identified previously as containing fewer neurons in autism. Individuals with autism exhibited a loss of cerebellar granular and Purkinje cells. Using the Western blot technique to measure differences in this regulatory neuronal protein in cerebellar cortical tissue, they found reductions in Bcl-2 levels in the brains of adults diagnosed with autism that fell below the control levels. In humans, the amount of Bcl-2 varies over the life span. These variations determine the risk of atrophy and occurrence of neurodevelopmental disorders including autism. If it was found that a reduction in Bcl-2 levels occurred in early fetal development, it would provide evidence for the Bauman and Kemper's hypothesis that the pattern of cerebellar histological abnormalities was a result of an insult in the first or second trimester of fetal development (94). However, such a study during the fetal period may be impossible. In a related finding, Fatemi et al. (2001) reported an increase in p53 protein in parietal cortex that correlated inversely with Bcl-2 levels. P53 is a tumor suppressor protein that regulates among other cellular events the cell cycle, DNA repair and apoptosis (95). The abnormal ratio of expressed Bcl-2 controlling cell proliferation to p53 involved in apoptosis suggests a greater potential for cell death in the autistic brain secondary to various cell regulating influences (96). As this abnormal ratio was identified in the parietal cortex, an explanation for language and visuospatial integration difficulties in the disorder may now have some histochemical explanation.

There are several known brain trophic factors that have been investigated including Reelin, and GABA that may have implications for the pathogenesis of autism.

Reelin is a secretory extracellular matrix protein whose function in the fetus may be to guide neurons and glial cells to their appropriate positions in the brain and later in development to participate in facilitating memory, cognition and neuronal plasticity through effective arborization (97). An animal model for understanding the function of reelin exists. The Reeler mouse has a genetic makeup containing a specific mutation resulting in a demonstrated reduction in the Reelin protein. The animal demonstrates abnormal neuronal cytoarchitecture, stereotypies and cerebellar hypoplasia suggesting traits sometimes found in the human with autism. However, viral infection in the midterm pregnant mouse also showed reduction in reelin levels with similar abnormal cyto-architecture (98). In humans, a relationship has been found between a specific polymorphism of the Reelin gene and affected individuals with autism (99). Fatemi et al. carried this line of investigation further. This group found a reduction of Reelin and its isoforms in the cerebellar cortex of autistic subjects (100) and in the frontal region (97), but also demonstrated a significant reduction in one component of blood Reelin, the 410 k Da species, not only in the affected individuals but also in all parents and normal unaffected siblings (101). Reelin has been mapped to chromosome 7, has as described above, important implications for neuronal cyto-architecture in places in the brain that have been shown to be histologically abnormal and reduced levels have been found in the blood of families with an affected individual, and implicated in other neurodevelopmental disorders. Potential for clinical testing and manipulation of levels with medications makes Reelin an intriguing target for future treatment. Neurotransmitter abnormalities in autism including abnormalities of the glutamate (increased) and gamma-aminobutyric acid (GABA) (decreased) system have been reported by several groups (102, 103). Possible related findings include a reduction in the rate limiting enzyme glutamic acid decarboxylase which is responsible for normal conversion of glutamate to GABA. Fatemi et al., (104) showed that two isoforms of glutamic acid decarboxylase (GAD), 65 and 67 kDa were reduced in two important areas of the autistic brain namely the cerebellar and parietal cortex. A decrease in this enzyme is likely to decrease the amount of inhibitory neurotransmitter GABA and cause an increase in excitatory neurotransmitter glutamate. The clinical implications of this may be in the increased rate of seizures and heightened sensory arousal systems that are problematic in this disorder. GAD 67 mRNA has recently been

reported to be significantly reduced in the brains of individuals with autism to support the above-mentioned studies (105). Blatt also showed that the number of GABA receptors in the hippocampus in the brains of four autistic adults were reduced connecting back and adding to the histocellular work of Bauman and Kemper and their findings of abnormalities in the same region (106). More recently, additional work has expanded on the GABAergic deficits in various brain areas in autism as well (203–205).

As intriguing as these findings are, results need replication. Also, how neuroregulatory proteins may themselves be regulated by either or both environmental and genetic factors awaits continued research exploration. The current research in neuroregulatory proteins may lead to one of the sought for mediating steps between genetics, environment and neuronal distortions and the phenomenology of ASD.

20.7. Immunological Abnormalities

While abnormal neuronal architecture appears implicated in the biological underpinnings of autism, it is not clear that these findings are driven directly by genetic or environmental factors. Their action may be mediated by other cellular mechanisms including inflammatory processes. For example, a genetic predisposition to a particular type of viral infection may set in motion, at a critical neurodevelopmental period, another physiological process that leads more directly to CNS pathology. Some evidence suggests that an immunological diathesis may be the intermediary step upon which genetic or environmental toxins act to disrupt the CNS . Vargas et al., (107), noted that microglia and astroglia appear to be activated in ways that were suggestive of an inflammatory response. Pliopys et al., (108), found antibodies directed at endothelial cells, neurofilaments and myelin basic protein. Supporting evidence for immunological activation was presented by Ahlsen et al., (109), with the increase in the level of Glial fibrillary acidic protein, a marker of glial activation in the cerebrospinal fluid of children with autism and by Fatemi's group in the superior frontal, parietal and cerebellar cortices of autistic subjects (110).

Serotonin binding sites have been implicated as targets of antibodies from an immune response to viral infection (111). Social deficits related to prenatal exposure to common viruses occurs in animal models (112). Further evidence for susceptibility to viruses due to impaired immune function leading to increased susceptibility to viral infection is present but sketchy in its depth. The reduction of natural killer cell cytotoxicity is a twenty year-old finding (113). This was confirmed subsequently by Gupta (114), who also found lower levels of IL 2, and IFN-gamma. This line of research suggests a chain of events and organismal susceptibilities leading to autistic phenomenology. It is intriguing to consider a genetic predisposition to poor immunological functioning that facilitates susceptibility to viral infections resulting in altered brain neurotropic factors leading to the disorder. Creating links between separate domains of study will necessitate interdisciplinary efforts to weave a coherent evidence-based pathophysiology.

20.8. EEG

20.8.1. Seizures and EEG

The etiology of seizures in autism is unknown but probably stems from the neurodevelopmental brain abnormalities that have been repeatedly documented. Seizures are common in ASD, occurring in about 20–30% of the patients (115) often present by adolescence. An even larger segment have abnormal brain electrical patterns. EEG abnormalities are present in 8–72% of this population (115–120). Various studies have shown the most frequent sites of the epileptiform abnormalities are localized over the temporal and frontal regions (117, 118, 121). Various EEG abnormalities have been reported in different studies including focal sharp waves, multifocal sharp waves, generalized spike wave complexes and generalized paroxysmal fast activity (117, 121). This lack of anatomical and electroencephalopathic specificity reduces the role of EEG as a screening or clinical tool in the assessment of ASD.

The clinical or prognostic implications of seizures in the disorder are not clear. About one third of autistic children undergo a developmental regression, after what appears to be a fairly healthy start to their lives. Loss of function related to language, communication and behavior ultimately fulfills ASD criteria (119). But this profound change may not be associated with EEG changes. There are conflicting results linking autistic regression, epilepsy and EEG abnormalities (119, 122). Alternative thinking points to seizures being more clearly related to mental retardation in ASD with a significant association between mental retardation and epilepsy (122). Finally, one possible research finding explaining the high seizure rate in individuals with autism is the decreased production of GABA. GABA is an important anti-excitatory neurochemical in the CNS whose reduction may account for the presence of seizures in individuals with autism (104, 203–206).

20.9. Epidemiology

The frequency of the disorder appears to be changing (123). The causes include increased case finding, changes in definition and diagnostic criteria and the possible effect of entitlements and school supports for the person diagnosed (126, 128–130). Additionally, stress of immigration, immunological etiologies, epigenetic factors and environmental toxins have all been implicated. An epidemiological survey for the more narrowly defined autism phenotype suggested a prevalence rate of 10 per 10,000 (124). This doubles the prevalence rate of 4 to 6 per 10,000 reported thirty-five years ago (125). The DSM IV diagnostic category of pervasive developmental disorder contained two disorders of very low rates, childhood disintegrative syndrome with an estimate of 0.2 per 10,000 and Rett's syndrome with a prevalence of 0.65 per 10,000 girls (207). A flurry of contemporary population studies have been completed with the Centers for Disease Control leading the way. With each subsequent effort larger numbers and more sophisticated identification methods were used. To capture more representative sample parental surveys were supplemented with cases identified from school records. The 2008 surveyors visited 14 sites throughout the U.S. and estimated the prevalence of ASD to be 11.3/10,000 children (127).

20.10. Treatment

Interventions for autism need to be as eclectic and disparate as the multiple features of the disorder. Cognitive impairment, language and social deficits and behavioral problems all need to be considered in treatment planning. Comprehensive treatment plans may include strategies for remediating the language and social disabilities as well as approaches for rigid and narrow behavioral repertoires. There are, as well, a myriad of other issues for which a parent will request assistance from a psychiatrist. Identifying and providing treatment guidance for a variety of common comorbid psychiatric disorders such as ADHD, obsessive compulsive traits and depressive disorders are mainstays of work with families. Another set of issues includes: seizures, insomnia, restricted range of behaviors such as contracted food choices leading to nutritional concerns and gastrointestinal related issues such as diarrhea, rectal digging, fecal smearing, encopresis and constipation. Common presenting challenges needing behavioral treatment approaches for excess and disruptive behaviors include self-injury, property destruction and aggression towards peers, siblings and adults, inconsistent sensory reactions, aggression and inappropriate sexual behaviors. In addition, parents raise service related questions such the adequacy and type of school services, and advice and assistance in navigating and accessing mental health community support and related services. And finally, the affected child's influence on sibling's psychological development and family functioning and the personal and financial dilemmas involved in payment for unique treatment approaches, are some of the thorniest parental concerns. Clearly the physician must be well versed in a variety of medical, behavioral, alternative, complementary, supportive, educational treatment approaches as well as knowledgeable about access to local community resources of the system of care in order to be helpful to the caregiver and affected individual. Referral to specialized services is necessary and not uncommon.

Guidelines for the assessment and treatment for individuals with ASD can be found in a recent report by the American Academy of Child and Adolescent Psychiatry (131). A developmental basis for the treatment of ASD is consistent with all other child mental disorders. Creating developmental progress in a child with ASD involves accurate assessment of baseline abilities, marshalling family and community resources, picking targets of treatment with functional outcomes and estimating the probability and extent of response to each intervention. Expectations for short and long term response need to be addressed.

Patient characteristics that are accurate indicators of response to treatment are poorly understood. In some cases, extensive intervention with multiple modalities and with high intensity, impacting several areas of disability, may seem to have little effect. At other times progress is surprising. Although some general guidelines may be helpful in predicting outcome such as onset of and extent of communicative speech, degree of cognitive delay, presence of seizures and degree of receptive language, these indicators of outcome may be much less reliable predictors of response or functional outcome when applied to a specific child. Developmentally appropriate strategies using educational and or behavioral methods often delivered in a special program within a school system under the rubric of an individual educational plan are the mainstay of community based interventions. Public Law 105-17 known as the Individuals with Disabilities Education Act identifies autism as a covered disability. Many useful services include early identification and assessment, transportation, speech-language pathology, audiology, psychology, counseling, physical and occupation therapy, medical services for diagnosis, social work services in school, assistive technology, adapted physical education, parent training and counseling, and preparation for post school activities. Some of the characteristics of effective in-school interventions for language and social skill building are curriculum driven and learning theory based. Such strategies for language and social skills building can be organized and mandated within the affected child's individualized education plan. Behavioral interventions using reward

contingencies are commonly used as well. Funding for such programs however and access and availability vary by community, school and strength of local advocacy. Medical interventions delivered by experienced practitioners can also vary because of restrictions built into funding sources, availability of local expertise and the logistics involved in delivering care to children with special needs. The role of the physician in delivering treatment can be extensive as in the case of a youngster with a seizure disorder or comorbid psychiatric disorders or may be advisory or best described as "ongoing monitoring", for interventions that target for example, language delays. As ASD is a lifelong disability, coordination of care over a lifetime by the health care community is essential towards accomplishing an efficient and rational use of resources and informed treatment planning.

20.10.1. Overview of Behavioral Treatments

Behavioral and educational interventions should be the first interventions applied to reduce excess and disruptive behaviors and to promote skills that support normal development. Stepwise discrete learning skill training for language and social functioning acquisition is one target of behavioral interventions that promote educational objectives. Behavioral approaches are useful for specific aspects of functioning that have import to increase quality of life such as toileting and other self-care. A different focus of behavioral intervention is concerned with the reduction of problematic behavior such as self-injury, aggression and destructive behavior, and limiting disruptive behavior such as screaming or excessive fluid intake.

The techniques of applied behavioral analysis which will evaluate the context and sequence of behaviors that lead to these behavioral events is sophisticated, specific, non punitive and effective. The role of the physician is both narrow and wide. As the expert who can consider multiple needs at many levels directing assessments of a variety of medical, educational, and supportive services, they have an overarching view of care. As an expert in the use of medication they contribute to the care of comorbid mental health problems and medical problems such as seizures and constipation. They advise, consult and facilitate access to behaviorists providing interventions for behavior management. There are a host of problems that families of ASD individuals face that include hyperactivity, sleep disorders, disorders of appetite, aggression, self-injury, perseverative behaviors, teeth grinding, constipation, diarrhea, and seizures. These problem behaviors have effective treatments that are best addressed by a team of experts. Management of these difficult problems in the ASD individual is key to improving and sustaining a better quality of life and functioning for the affected child and his or her family.

20.10.1.1. Interventions for Language Deficits

Behavioral strategies to increase communication include teaching sign language using picture representations or adapting computer aided software that creates voice based on a persons visual selection. Each has been studied and there is some evidence that they may facilitate the acquisition of verbal language (132, 133, 136). Applied Behavioral Analysis has a long history of applicability in this area. Although controversial because of the enormous time and resources required and because studies analyzing its efficacy sometimes had significant limitations which curtailed generalizability, its more recently trained practitioners are very skilled and resourceful (134, 135).

20.10.1.2. Social Skill Acquisition

Multiple approaches to tackle social intelligence, a fundamental hallmark of the autistic disorder, are available. The clinician might recommend interventions such as Social Stories and Priming and Pivotal Response Training (137, 138). Social stories use a written script that focuses on a very narrow and specific aspect of social interaction. The stories are very detailed and describe the social event to be mastered, the appropriate response expected and the perspective of the individuals who participate in an effort to reduce off putting behaviors and perseverative speech. Priming considers a situation or event that would usually result in challenging behavior by the patient with autism. Immediately preceding the event leading to the negative behavior a prosocial behavior is presented followed by a reinforcer. The behavior to be imitated might be modeled by a peer or could be captured on videotape for timely representation (139). Pivotal Response training requires a behavior to be exhibited by a highly motivating model and sets out a prescribed sequence of learning enhancing behaviors to influence the target child. In addition to a high degree of motivating stimuli that are brought to bear on each encounter the model demonstrates the pivotal behavior to be learned. Although complex in its training of the "model" peer and the need for supervision by trained staff, there is some evidence that this approach will extend taught language and social behaviors to other settings (140).

20.10.2. Psychopharmacology

Various psychotropic medications are used to treat problems associated with autism spectrum disorders. These medications generally are not helpful for the core symptoms but can be effective for associated symptoms including but not limited to irritability, aggression, self-injurious behaviors, hyperactivity, impulsivity, stereotypies and repetitive behaviors, and sleep problems. Currently there are no medications approved by FDA to treat ASD. Successful management requires a raft of essential services including speech and language therapy, social skills training, appropriate school and educational services, structured environments, occupational therapy and behavioral interventions along with medication evaluation and treatment and psychoeducation and support to the family. Various surveys show that psychotropic medications are commonly used as part of a treatment program. The frequency with which they are used range from 45% to 55%, with antidepressants, antipsychotics, stimulants and antiepileptic medications the most commonly prescribed medications (141–143).

20.10.2.1. Stimulants

Concern about the use of stimulants for ASD has subsided. A better understanding of the commonalities of the neurodevelopmental disorders of ADHD and ASD and studies demonstrating their safe but judicious use are now available. Stimulants are prescribed for ASD to manage hyperactivity, impulsivity and attentional problems. Studies have shown that response rate with stimulants for these symptoms are much lower in ASD as compared to children with ADHD. In an open label study including 13 subjects with pervasive developmental disorders, methylphenidate, given as a one-time dose, resulted in 4 children rated as improved, 4 as unchanged and 5 subjects exhibiting increased hyperactivity, stereotypes, dysphoria who were rated as minimally or much worse. Eight of the children without side effects entered into a 12-week open label trial. The majority showed improvement on measures of hyperactivity and impulsivity (144). In a placebo-controlled double blind cross over study, 8 out of 13 children with autism showed at least a 50% reduction of symptoms in response to methylphenidate on the Conners' Hyperactivity Index (145). As part of a multiple pharmacological study on autism supported by the National Institute of Mental Health, the Research Units on Pediatric Psychopharmacology (RUPP) Autism Network completed a double-blind, placebo-controlled, crossover trial of methylphenidate with children aged 5 to 14 years. Interestingly there was improvement noted but the effect size was lower than that seen in ADHD children. Also, only half of the group was much improved or very much improved. About one in five children could not tolerate the medication (146). ADHD symptoms may respond to stimulant medications although dosing needs to be individualized more carefully than for children with ADHD alone.

20.10.2.2. Selective Serotonin Re-Uptake Inhibitors (SSRIs)

This class of medications is one of the most commonly used in this population. Serotonin re-uptake inhibitors are often considered for treatment of stereotypies and repetitive behaviors that interfere with day-to-day functioning. Children with ASD are often very sensitive to environmental change and even low levels of sensory stimuli. In that respect, they appear to have excessive anxiety-like problems. ASD may predispose to mood and other internalizing disorders. Diagnostic precision is hampered because subjective symptoms may not be elicited easily and overlap with the core features of ASD, for example repetitive behaviors confounds assignment to a compulsive disorder. In cases where an inventory of symptoms fails to fulfill all the criteria, diagnostic recommendations for Unspecified Depressive Disorder, Unspecified Anxiety Disorder or Unspecified Obsessive-Compulsive and related Disorders can and should be made.

In a placebo controlled cross-over trial of fluoxetine in 45 developmentally delayed ASD children and adolescents, fluoxetine was superior to placebo in reducing repetitive behaviors assessed by CY-BOCS Compulsion Scale (147). In a 12-week, double blind, placebo, randomized controlled study; fluvoxamine was shown to be superior to placebo in 30 adults with autistic disorder. The response rate for the fluvoxamine arm was 53% for improvement in repetitive thoughts and behaviors, and repetitive language use, as compared to no change for placebo (148). In another double blind study involving clomipramine (a tricyclic antidepressant with serotonin reuptake inhibition) desipramine and placebo, clomipramine was superior to both placebo and desipramine on ratings of autistic symptoms (including stereotypies), anger, and compulsive, ritualized behaviors (149). Several less rigorously designed studies show similar positive response to fluoxetine, sertraline, fluvoxamine, citalopram and escitalopram (150–157). The side effect profile in these studies were somewhat atypical, as compared to groups in which autism was not part of the diagnostic picture, and included agitation, insomnia, aggression and hyperactivity.

20.10.2.3. Tricyclic Antidepressants

Although the main features of autism are deficits of high-level neurocognitive competencies i.e. language and social interactive skills, one of the simpler to asses symptoms is stereotypies. These movements quickly call attention to the child and raise the question of an ASD. Stereotypies however are not *sine quo non* for ASD and can be difficult to distinguish from tics and tic disorder. Repetitive movements including head banging, hand flapping and finger flicking are not uncommon and may warrant intervention because of concussive damage or damage to joints caused by the behavior and interference with educational programming due to time spent in distracting stereotypic behaviors. Clomipramine has been used to treat stereotypies by two research groups with significant reduction in the target behavior (158, 159).

20.10.2.4. Typical Antipsychotics

Before the era of atypical antipsychotics, traditional neuroleptics were widely used to address behavioral issues associated with autism. Among traditional neuroleptics, haloperidol is the most studied. In various double blind and controlled studies haloperidol was effective in decreasing behavioral symptoms, irritability and hyperactivity (160–162). Careful monitoring is required due to multiple risk factors for potential long-term serious side effects of this class of medication including tardive dyskinesia and other adverse events. Surveillance for both withdrawal dyskinesia and tardive dyskinesia is obligatory in this population (163, 164).

20.10.2.5. Atypical Antipsychotics

Atypical or second generation antipsychotic use is widespread in ASD. There are encouraging studies showing reduction in aggression, self-injurious behaviors, impulsivity, hyperactivity and repetitive behaviors. Some uses, however seem questionable for example their use in the treatment of sleep disorders in this population. Experience has now taught us that we have exchanged one set of terrible side effect of the "typicals" namely persistent motor disorders for very serious and likely life shortening metabolic illness. Advice for carefully monitoring weight gain and metabolic abnormalities does not avert these consequences. Diet and exercise which are effective in managing these side effects are not easily operationalized interventions. Behavioral interventions, low medication dose and a medication exit plan should be part of the planning before atypicals are started.

Risperidone is the most studied atypical antipsychotic agent in this population. There are numerous short and long term controlled and open label studies showing efficacy of risperidone in autistic children and adolescents (165–170). The landmark multisite, randomized, double-blind study conducted by Research Units on Pediatric Psychopharmacology (RUPP) Autism Network, demonstrated a positive response to risperidone (209). The study involved 101 autistic children with severe tantrums, aggression, or self-injurious behavior (82 boys and 19 girls, mean age 8.8 years, age range 5–17 years). Children were randomly assigned to receive risperidone (49 children) or placebo (52 children) over 8 weeks. The mean dose of risperidone was 1.8 mg/day (range 0.5 to 3.5 mg/day). Treatment with risperidone for 8 weeks resulted in 56.9% reduction in irritability as compared to a 14.1% decrease with placebo. The Clinical Global Impression Improvement (CGI-I) scale showed 69% (34 of 49 children) in the risperidone-treated group as responders versus 12% (6 of 52) in the placebo group. In two thirds of the children with positive response to risperidone at 8 weeks, the benefit was maintained at 6 months. Average weight gain with risperidone was 2.7 kg as compared to placebo at 0.8 kg. Other side effects which were more common in the risperidone group included: increased appetite, fatigue, drowsiness, dizziness and drooling (166).

Preliminary results with aripiprazole were promising in a case series involving 5 youth with pervasive developmental disorders and maladaptive behaviors. No significant adverse effects were reported (171). More rigorous studies followed. Aripiprazole showed some interesting differences compared to risperidone. Not only irritability but hyperactivity and stereotypy were also positively impacted. Effects were measured on the Aberrant Behavior Checklist and the changes appeared to be statistically and clinically meaningful. Weight gain, metabolic issues and a trend towards extrapyramidal symptoms consistent with the adverse side effect profile for this medication was also found. Not reported for risperidone but measured were changes on the Yale Brown Obsessive Compulsive scale which showed non statistically significant change (172, 173).

In two open label studies with olanzapine, positive response was documented on the Clinical Global Impression Scale. Mean dose of olanzapine was about 8 mg/day. Major side effects were weight gain and sedation (174, 175). However in a placebo controlled randomized small trial that may not have been sufficiently powered, no significant changes were evident on the CGI measure (176).

The response to quetiapine in two open label studies were not encouraging. In one 16-week open label trial involving 6 children with autistic disorder and mental retardation, there was no statistical improvement from baseline to endpoint for the

group as a whole. Side effects were sedation, behavioral activation, increased appetite and weight gain (177). In another 12-week open-label study involving 9 youth with autistic disorder, only 2 out of 9 at study endpoint were considered responders to quetiapine on the Clinical Global Impression-Improvement (CGI-I) Scale (178).

Ziprasidone was investigated in an open label study involving 12 patients (9 with autism and 3 with pervasive developmental disorder not otherwise specified) treated for at least 6 weeks (mean duration 14.5 ± 8.29 weeks). The mean daily dose of ziprasidone was 59.23 ± 34.76 mg (range 20–120 mg). Six (50%) of the 12 patients were considered responders based on Clinical Global Impression Scale. Transient sedation was the most common side effect. No cardiovascular side effects were noted. Five patients lost weight, five had no change and one gained weight at study endpoint (179). Supporting these findings is another small open label study in adolescents with autism. Importantly the drug was weight neutral with some subjects losing weight. The QTc interval increased but was not clinically concerning. Seventy-five percent were considered responders based on the CGI with a mean dose of 98.3 ± 40.4 mg (180). Three FDA newly approved agents asenapine, iloperidone, and lurasidone, have not been studied either in a pediatric population or in ASD.

20.10.2.6. Anticonvulsants

Seizures may occur up to 70% in narrowly defined autism. Good seizure control is essential as complications from seizures confer morbidity and mortality. Thus, considerable clinical experience can be found with various antiepileptic medications in this population. Some of the anticonvulsants like divalproex sodium and carbamazepine may have an added advantage of helping with mood lability and behavioral issues. However, there is very limited data from controlled trials looking at the effectiveness of these agents for specific core symptoms of ASD. In a recent 13-week double-blind, placebo controlled study involving 13 individuals with ASD, sodium valproex was superior to placebo in reducing repetitive behaviors as measured by the Children's Yale Brown Obsessive Compulsive Scale (C-YBOCS; 181). In a retrospective study of divalproex sodium in 14 individuals with pervasive developmental disorders, 10 (71%) had a positive response. The mean dose of divalproex sodium was 768 mg /day (range 125–2500 mg/day) and it was generally well tolerated (182).

Response to levetiracetam was positive in an open label study of ten autistic boys ranging from age 4 to 10 years old. Levetiracetam was effective in reducing hyperactivity, impulsivity, mood instability and aggression (183). In a controlled double blind study of this antiepileptic medication no improvement was noted in a wide range of symptoms found in this population (184).

In a double blind placebo controlled study involving 27 youth with autistic disorder, lamotrigine was not found to be effective as compared to placebo (185).

The overall poor response of this class of medications appears to confine their use to comorbid psychiatric disorders with known indications for treatment such as bipolar disorder.

20.10.2.7. Sympatholytics

The alpha adrenergic agonists clonidine and guanfacine are used in autistic children to help with hyperactivity, impulsivity and irritability. Transdermal clonidine was effective in reducing hyperarousal behaviors and improving social relationships in autistic individuals in a double blind, placebo-controlled study. Adverse effects included sedation and fatigue (186). In another controlled, double blind study involving 8 male children with autistic disorder; clonidine was modestly effective in reducing irritability and hyperactivity (187). In a retrospective analysis of 80 children with pervasive developmental disorders, guanfacine was effective in 19 (23.8%) of the children. Improvement was seen in hyperactivity, inattention, insomnia and tics. Guanfacine was well tolerated without significant effects on blood pressure or heart rate (188). Beta blockers are known to moderate aggressive behaviors in various populations and one study has considered use in a small study of youth with autistic disorder. In this open trial a beta blocker reduced aggression in autistic disorder (189).

20.10.2.8. Naltrexone

Opiate receptors have been implicated in the pathophysiology of self injury and autism (190). Naltrexone, an opiate antagonist, had been suggested for the treatment of this very troublesome behavior in autistic disorder. The studies have shown mixed response to naltrexone. Naltrexone had modest effect in reducing hyperactivity and improving social relatedness in small studies. Naltrexone was generally well tolerated without any negative effects on liver enzymes (191–194). Double blind, placebo controlled studies of naltrexone in autism failed to show any positive effects on communication, social interactions, stereotypies and self-injurious behaviors (195–197).

20.10.3. Unproven Treatments

There are advocates for a panoply of putative treatments. Caregivers can easily tap into a variety of informational sites. These continue to grow as the internet grows. Social media, blogs, web sites, for-profit and other alternative sites for homeopathic and nutritional substances and community and educational support groups and other casual communication networks make available the newest scientific developments as well as promises for a natural remedy for symptoms of ASD. To recount a few whose claims were proven false yet linger within the folklore of treatments includes: secretin (198), a gut enzyme, B6 and magnesium (199), and antifungal treatments (200) have failed to duplicate their early highly touted initial successes or had their theoretical position validated. Chelation therapy to remove mercury or other suspected toxins poses specific dangers of which caregivers need to be made aware. No peer-reviewed study has evaluated this potentially hazardous intervention. The list of complementary biological treatments includes B12, Folic Acid, dimethylglycine, tryptophan and tyrosine supplementation, cyproheptadine, D-Cycloserine, carnosine supplementation, Omega-3 Fatty Acids, and carnitine (201). Folic acid has emerged from this grouping with non causal evidence for mitigating risk for ASD when taken prior to and during pregnancy (208). The dose in this Norwegian survey of pregnant women was less than the now recommended dose of 400 μg. The incidence of ASD in the children born to mothers who took folic acid during pregnancy was reduced by half (208).

Assisting parents in evaluating the evidence for any of these and the next of many proposed unfounded treatments remains the responsibility of the clinician. Do no harm. Advocating for research in areas that have functional benefits such as early intensive behavioral programs and clinical trials targeting problems that alleviate symptoms and the family burdens for the care of children with ASD should be a part of each practitioner's efforts. In addition, generating a better understanding of the causes of the disorder through support for basic research will inform the first objective. A strategy that focuses research support in areas that have shown considerable promise such as early modifiers of brain development and epidemiological studies that track changes in incidence and the causes of these fluctuations should be part of a clinicians wider activity for his/her patients.

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21
Childhood Anxiety Disorders and Obsessive-Compulsive Disorder

Andrea M. Victor, Ph.D., Alexandra D. Zagoloff, Ph.D., and Gail A. Bernstein, M.D.

Abstract Anxiety disorders is one of the most prevalent diagnostic categories identified in children and adolescents. This chapter provides an overview of the epidemiology of childhood anxiety disorders and presents several pathways of etiology, specifically genetics, parent–child attachment, and neurobiology. Separation anxiety disorder, selective mutism, specific phobia, social anxiety disorder, generalized anxiety disorder, obsessive-compulsive disorder, and panic disorder are reviewed. Cognitive-behavioral therapy and psychopharmacology are summarized as effective treatment approaches for childhood anxiety disorders.

Keywords Childhood anxiety disorders · Separation anxiety disorder · Specific phobia · Social anxiety disorder · Generalized anxiety disorder · Obsessive-compulsive disorder · Panic disorder · Selective mutism

Epidemiologic studies document that anxiety disorders is one of the most prevalent categories of childhood and adolescent psychopathology (1). The amount and quality of research studies that provide data about childhood anxiety disorders are rapidly increasing. Childhood anxiety disorders is currently a topic of high interest to researchers and practitioners. Anxiety disorders are arranged differently in the DSM-5 (2) compared with the DSM-IV-TR (3). In the DSM-IV-TR, anxiety disorders were separated into two sections: the Anxiety Disorders section contained diagnostic criteria for panic disorder, agoraphobia, specific phobia, social phobia, obsessive-compulsive disorder (OCD), posttraumatic stress disorder, acute stress disorder, generalized anxiety disorder (GAD), and anxiety disorder not otherwise specified; and the section for Disorders Usually First Diagnosed in Infancy, Childhood, or Adolescence contained criteria for separation anxiety disorder (SAD) and selective mutism (SM). The DSM-5 again has two sections for anxiety disorders, but the disorders are grouped differently. The primary section is labeled Anxiety Disorders and includes the following diagnoses: SAD, SM, specific phobia, social anxiety disorder (formerly listed as social phobia), panic disorder, agoraphobia, GAD, substance/medication-induced anxiety disorder, anxiety disorder due to another medical condition, other specified anxiety disorder, and unspecified anxiety disorder. The second section is called Obsessive-Compulsive and Related Disorders and contains criteria for the following disorders: OCD, body dysmorphic disorder, hoarding disorder, trichotillomania (hair-pulling disorder), excoriation (skin-picking) disorder, substance/medication-induced obsessive-compulsive and related disorder, obsessive-compulsive and related disorder due to another medical condition, other specified obsessive-compulsive and related disorder, and unspecified obsessive-compulsive and

A.M. Victor, Ph.D.
Psychologist, Chicago Neurodevelopmental Center, Chicago, IL, USA
e-mail: avictor@chicagoneuro.org

A.D. Zagoloff, Ph.D.
Assistant Professor, Department of Psychiatry, Division of Child and Adolescent Psychiatry, University of Minnesota School of Medicine, Minneapolis, MN, USA
e-mail: zagol001@umn.edu

G.A. Bernstein, M.D. (✉)
Endowed Professor in Child and Adolescent Anxiety Disorders, Head, Program in Child and Adolescent Anxiety and Mood Disorders, Division of Child and Adolescent Psychiatry, University of Minnesota Medical School, Minneapolis, MN, USA
e-mail: berns001@umn.edu

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related disorder. This chapter begins with an overview of the epidemiology and etiology of childhood anxiety disorders, reviews the common childhood anxiety disorders, and then summarizes effective treatment approaches.

21.1. Epidemiology

There are several issues that make childhood anxiety disorders one of the most difficult areas to study in a representative sample (1). First, several of the disorders (e.g., panic disorder) are rarely found in general population samples. Second, there continues to be uncertainty regarding the distinctions among various childhood anxiety disorders. Finally, direct assessment of young children is difficult due to their lack of psychological awareness of symptoms associated with anxiety. Anxiety disorders in children and adolescents are among the most common mental health disorders in youth (4). The rate of anxiety disorders tends to increase as children get older and reach adolescence.

Epidemiologic studies with a short assessment interval and single-date collection report the lowest prevalence rates of childhood anxiety disorders, whereas, studies that implement a lifetime criterion with older adolescents result in the highest prevalence rates (1). As the length of time considered increases, prevalence estimates tend to rise. Reviewing several prevalence studies of anxiety disorders in children and adolescents, 3-month estimates range from 2.2 to 8.6% (5, 6), 6-month estimates range from 5.5 to 17.7% (7, 8), 12-month estimates range from 9.3 to 20.9% (9, 10), and lifetime estimates range from 8.3 to 27.0% (11, 12). These epidemiologic studies are primarily composed of samples of Caucasian children and adolescents. There is little known about the manifestation and presentation of childhood anxiety disorders across racial and ethnic groups. However, Lewis-Fernandez and colleagues (13) found a possible cross-cultural variability with lower rates of anxiety disorders in Asian and African-American individuals.

There is limited information regarding the prevalence of anxiety disorders in preschool-aged children. One study examined the prevalence rate of anxiety disorders in a community sample of 1,073 young children (ages 24–71 months) (14). The results indicated that 4- and 5-year-old children were more likely to be diagnosed with an anxiety disorder compared with children who were 2 and 3 years old (11.9% versus 7.7%). Prevalence rates varied across anxiety disorders, with 6.5% of children diagnosed with GAD, 2.4% with SAD, 2.3% with specific phobia, 2.2% with social anxiety disorder, and 0.6% with selective mutism (SM). There were high rates of comorbidity with other psychiatric disorders. African-American children were less likely to meet criteria for an anxiety disorder compared with children who were not African-American (6.4% versus 14.0%) (14).

Costello and colleagues (5) conducted the Great Smoky Mountains Study (GSMS) that allowed examination of the prevalence and continuity of psychiatric disorders in a sample of 4,500 children and adolescents. The children were 9, 11, and 13 years of age at intake and were evaluated annually until 16 years of age. The initial results indicated that 5.7% had a diagnosis of any anxiety disorder with the following prevalence rates across DSM-III-R anxiety disorders: 3.5% with SAD, 1.7% with GAD, 0.6% with social anxiety disorder, 0.3% with specific phobia, 0.17% with OCD, and 0.03% with panic disorder. Costello and colleagues (15) found lower 3-month prevalence rates of DSM-IV anxiety disorders in a more recent study using a smaller GSMS sample of 1,420 children and adolescents. The prevalence of any anxiety disorder was 2.4% and the rates for each individual diagnosis were: 1.0% with SAD, 0.8% with GAD, 0.5% with social anxiety disorder, 0.2% with specific phobia, and 0.2% with panic disorder. In addition, the overall prevalence of anxiety disorders was greatest in children 9–10 years of age (4.6%) and was the lowest at 12 years of age (0.9%). The diagnoses then increased in prevalence following 12 years of age. Specifically, the transition to adolescence resulted in an increase in social anxiety disorder in females only and an increase in panic disorder and GAD across genders.

Females are more likely to endorse an anxiety disorder compared with males; however, when gender differences are examined in each diagnosis, these differences tend to be small (1). Lewinsohn and colleagues (12) conducted the Oregon Adolescent Depression Project in order to examine prevalence rates in over 1,700 adolescents. Results showed that 2.8% of the adolescents endorsed at least one current anxiety disorder. Gender differences among the adolescents were explored by controlling for confounding factors (i.e., environmental stress, social support, family environment, self-esteem), and results continued to demonstrate a significantly higher prevalence rate of anxiety disorders in females compared with males. This gender difference was present by 6 years of age, as determined by retrospective reports, at which time twice as many females compared with males had already experienced an anxiety disorder. The mean age of onset did not significantly differ between males ($M = 8.5$ years, $SD = 3.8$) and females ($M = 8.0$ years, $SD = 3.9$).

Mann and colleagues (16) screened over 3,000 adolescents for symptoms of anxiety and mood disorders and found that approximately 19% of adolescents reported probable anxiety and mood disorders. Several factors contributed to a higher likelihood of symptom endorsement. Adolescents who reported harmful drinking, substance use problems, and gambling problems were significantly more likely to endorse symptoms of an anxiety and/or mood disorder. A family history of involvement with Child Protective Services also increased an adolescent's likelihood of reporting problematic symptoms associated with anxiety and depression.

21.2. Etiology

21.2.1. Genetics

Pediatric anxiety disorders have complex genetic inheritance patterns involving multiple genes, rather than single genes with major causative effects. There is evidence that early-onset anxiety disorders have higher heritability rates than adult-onset anxiety disorders. The early-onset anxiety disorders have moderate heritability estimates of 20–65% (17–19). Pediatric OCD has heritability estimates in the upper part of the range (i.e., 45–65%) (18, 19). The estimates for heritability of anxiety disorders are similar to those for depressive disorders, but lower than for ADHD, bipolar disorder, and autism (20). The moderate estimates of heritability suggest that environmental factors (e.g., insecure parent–child attachment, psychosocial stressors) also play a substantial role in pediatric anxiety disorders (20).

There are two methods to localize and identify susceptibility genes. The first approach is linkage analysis that investigates the location of the genes of interest and the second is the association analysis that examines if there is a correlation between a specific genetic variant and a given anxiety disorder. Association studies usually employ the case–control approach that evaluates whether a genetic variant is more frequent in the identified cases compared with controls. Case–control studies can examine genes based on biological hypotheses (biological candidates) or via position on the genome as identified via linkage studies (positional candidates).

Candidate genes of interest for OCD and panic disorder have been investigated and supported by research. Six independent association studies identify the glutamate transporter gene, SCL1A1, which is located on chromosome 9p, as important in OCD (21–26). In panic disorder, catechol-O-methyltransferase (COMT) has been identified as the most promising candidate gene (20). Both of these genes (SCL1A1 and COMT) play a role in neurotransmission.

Interestingly, genetic influences may be dynamic across time. In a longitudinal twin study, youths with specific phobias were assessed across four developmental time periods between ages 8 and 20 (27). Heritability estimates were 50–69% at each assessment point, but contributory factors changed across time. In that study, it appeared that "…different genes may have variable impact on anxiety phenotypes across the lifespan" (20, p. 490). Since genetics plays such an important part in pediatric disorders, obtaining a thorough family history is essential in identifying which youths are at higher risk for developing anxiety disorders.

21.2.2. Parent–Child Attachment

Another factor that appears to contribute to anxiety disorders in children is insecure attachment between mother and child. Attachment theory suggests that predisposition toward anxiety can be alleviated or exacerbated by the nature of the attachment between child and primary attachment figure (28). In a study beginning in the third trimester of pregnancy, mothers and their children were studied prospectively (29). At 12 months of age, attachment pattern was evaluated with the Ainsworth Strange Situation Procedure, and, at 17.5 years of age, anxiety was assessed with a diagnostic interview. It was found that an anxious-resistant attachment (a type of insecure attachment) at 12 months was associated with anxiety disorders at age 17 years. The regression analyses suggested that anxious-resistant attachment was a stronger predictor of future anxiety diagnoses than the child's temperament or maternal history of anxiety.

21.2.3. Neurobiology

21.2.3.1. Anxiety Disorders

In anxiety disorders (e.g., SAD, GAD, and social anxiety disorder), the amygdala and the prefrontal cortex (PFC) are the key components of the fear circuitry. These two areas of the brain are interconnected in the fear circuitry and the PFC modulates the amygdala's responses to fear (30). It has been hypothesized that in children with anxiety disorders, fear production is too strong and fear regulation is too weak and these differences are associated with abnormalities in the brain circuitry (30).

Neuroimaging studies support that the brain dysfunction in anxiety disorders is based in the amygdala and multiple areas of the PFC. Children with GAD or panic disorder compared with healthy controls showed an increase in amygdala activation during the viewing of fearful faces (31). The level of amygdala activation correlated positively with the severity of anxiety (31). In a small functional magnetic resonance imaging (fMRI) study that compared adults with panic disorder ($n=6$) and healthy controls ($n=8$), participants with panic disorder showed significantly greater activation in the posterior cingulate cortex and dorsolateral PFC when viewing threat-related words (32). Adolescents and adults with social anxiety disorder compared with healthy controls showed an increase in activation in the amygdala and ventromedial PFC during the viewing of fearful faces (33). Youths with social anxiety disorder and those at risk for social anxiety disorder (i.e., youths with behavioral inhibition) also demonstrate changes in amygdala activation when exposed to anxiety-producing stimuli (34). These studies indicate that

children with anxiety disorders and those at risk for anxiety disorders exhibit dysfunction in the amygdala and PFC areas during tasks designed to probe the fear circuitry.

21.2.3.2. OCD

Neuroimaging studies of children and adolescents with OCD show abnormalities in the fronto-striatal-thalamic circuitry (FSTC). This circuit connects neurons in the frontal cortex, striatum (i.e., caudate, putamen), thalamus, and then back to the frontal cortex (35). Task fMRI studies show that youths with OCD compared with healthy controls exhibit lower levels of brain activation in FSTC regions (36, 37). A review of neuroimaging studies concludes that findings from a variety of imaging techniques implicate abnormalities in FSTC in pediatric OCD (38).

Recent advances in neuroimaging that assess brain connectivity allow for sophisticated understanding of neural networks. There has been a growing interest in resting-state functional magnetic resonance imaging (R-fMRI) to assess functional connectivity. This approach uses the covariance of the fluctuation pattern of blood-oxygen-level-dependent signals between brain areas to represent functional connections (39). Fitzgerald and colleagues (40) compared functional connectivity among four developmental age groups (children, adolescents, young adults, and older adults). They demonstrated that children with OCD show lower connectivity between the rostral anterior cingulate cortex (ACC) and dorsal striatum (associated with greater OCD severity) and between the dorsal ACC and medial dorsal thalamus. Using R-fMRI, Bernstein and colleagues (41) found lower functional connectivity in several connections in the FSTC in adolescents with OCD compared with healthy controls. In addition, there were significant negative correlations between OCD severity on the Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS) (42) total scores and a few of the FSTC connections in OCD participants (41). These findings support pediatric OCD as being associated with lower functional connectivity in the FSTC.

21.3. Separation Anxiety Disorder

Separation anxiety is a normal developmental process that results in appropriate distress upon separation from attachment figures (43). Separation anxiety typically occurs in children from 6 to 30 months of age and generally intensifies when the child is 13–18 months old. The frequency and intensity of separation anxiety normally decreases between ages 3 and 5 years due to the child's increased cognitive capacity to understand that separation is temporary. Studies suggest that a diagnosis of SAD is not stable throughout early childhood, and many children shift between clinical and nonclinical symptoms of separation anxiety (43).

21.3.1. DSM-5 Criteria

Separation anxiety is considered clinically significant when it exceeds developmental norms and is associated with impaired functioning. In the DSM-IV-TR, SAD was only diagnosed in youth and could not be diagnosed in adults. However, in the DSM-5, SAD can be diagnosed in children and adults. According to the DSM-5 (2), the essential feature of SAD is excessive and persistent anxiety about being away from home or attachment figures (i.e., parents, grandparents, other primary caregivers, or siblings). Common characteristics of individuals diagnosed with SAD are worry about harm occurring to attachment figures or themselves when separated, reluctance or refusal to attend school, nightmares about separation from attachment figures, and complaints of physical symptoms when separation occurs or is expected. In order to be diagnosed with SAD, the anxiety must persist for at least 4 weeks in children and 6 months in adults and cause significant distress or impairment in social, academic, or other areas of functioning.

21.3.2. Clinical Presentation

SAD has a prevalence ranging from 1 to 5% in children and adolescents, with higher prevalence rates in children compared with adolescents (5, 44, 45). Some studies suggest that SAD is more common in females (46), whereas other studies suggest that there are no significant gender differences (5, 47). An adult form of separation anxiety disorder (ASAD) has been described (48) with an estimated lifetime prevalence of 6.6% (49). Silove and colleagues (50) identified ASAD in 23% of all diagnoses made in an adult anxiety clinic with the diagnosis more common in females compared with males. In most cases, individuals with ASAD have a history of SAD during childhood. Since ASAD is fairly new in the psychiatric literature, there is limited information about the prevalence, course, and outcome.

Symptom presentation in SAD appears to manifest differently across the age span with younger children exhibiting more symptoms compared with older children (51). Children ages 5–8 years most commonly report anxiety regarding harm to attach-

ment figures and school refusal. As children reach 9–12 years, symptoms typically manifest as significant distress during times of separation. During adolescence, school refusal and somatic complaints are most common. Symptoms of ASAD are typically similar to childhood SAD (50). Individuals with ASAD engage in behaviors to maintain close contact with their attachment figures due to intense fears that something bad will happen to their attachment figures.

In a study of 199 children (ranging from 8 to 13 years) diagnosed with SAD, GAD, and/or social anxiety disorder, children with SAD had the greatest mean number of comorbid diagnoses (52). The most frequent comorbid diagnoses with SAD included GAD in 74%, specific phobia in 58%, attention-deficit/hyperactivity disorder (ADHD) in 22%, social anxiety disorder in 20%, and oppositional defiant disorder (ODD) in 12%. The likelihood of comorbid mood disorders was lower in children with a primary diagnosis of SAD (2%) compared with children with a primary diagnosis of GAD (17%) or social anxiety disorder (15%). Since ASAD is still emerging in the psychiatric literature, limited information is known about comorbidity.

21.3.3. Course and Outcome

Parental depression, parental panic disorder, and strong stranger anxiety during infancy may be early predictors of SAD in childhood (53, 54). The mean age of onset of SAD typically falls between 7 and 9 years (47). Kearney and colleagues (43) completed a longitudinal study of 3-year-old children ($N=60$) with clinical, subclinical, or nonclinical levels of separation anxiety. Results indicated that many children diagnosed with SAD exhibited a decline in symptoms after a 3.5-year time period and shifted towards subclinical and nonclinical symptoms. The course and short-term outcome of SAD were further examined using a community sample of twins ranging in age from 8 to 17 years ($M=10.9$ years) (55). After an 18-month follow-up period, 20% of children continued to meet criteria for SAD. Children with persistent SAD differed from children with more transient episodes of SAD in several ways. Predictors of persistent SAD included a comorbid diagnosis of ODD, impairment associated with ADHD, and maternal marital dissatisfaction. At 18-month follow-up, children with persistent SAD were more likely to have a comorbid diagnosis of overanxious disorder (OAD), the former label for GAD, and a new diagnosis of depressive disorder.

Lewinsohn and colleagues (56) completed a longitudinal study to improve understanding of the course of SAD, as well as the relations to subsequent psychiatric diagnoses. Participants with a previous SAD diagnosis were more likely to develop a depressive disorder and panic disorder during early adulthood. Seventy-five percent of participants with childhood SAD had an episode of depression and 25% developed panic disorder during early adulthood. A previous SAD diagnosis was not related to the subsequent development of other anxiety disorders or substance use disorders.

There is conflicting evidence regarding whether SAD may be specifically related to later development of panic disorder. Approximately 50–75% of children and adolescents with early-onset panic disorder have a previous or comorbid diagnosis of SAD (57, 58). Research has suggested that a history of childhood SAD may be related to a specific heritable early-onset form of panic disorder (59). One study completed a 7-year follow-up of youth who had participated in treatment for an anxiety disorder during childhood (60). A childhood diagnosis of SAD was predictive of a greater number of anxiety disorders 7 years later compared with a childhood diagnosis of GAD and social anxiety disorder. Participants with a primary diagnosis of SAD had a higher rate (27.8%) of panic disorder at follow-up compared with participants with a primary diagnosis of social anxiety disorder (12.5%) and GAD (14.3%). Studies suggest that SAD is likely linked to adult anxiety disorders in general (61), with particular focus on the relationship between SAD and panic disorder (59, 60, 62).

Robertson-Nay and colleagues (62) completed a twin study that compared the relation between SAD and adult onset panic attacks with the relation of OAD and adult onset panic attacks. Results supported a specific genetic etiological connection between childhood SAD and adult onset panic attacks that did not occur in childhood OAD. Findings indicated that a genetic vulnerability likely leads to the presence of SAD symptoms in childhood. This vulnerability then contributes to the development of panic attacks in adulthood, which suggests that childhood SAD may be a predictor for later panic disorder.

Based on the current literature, it appears that early separation anxiety symptoms place individuals at a greater risk of developing later psychopathology, especially related to anxiety and depressive disorders. However, the longitudinal data do not provide evidence for causality. Childhood SAD may be a causal factor for later psychopathology or alternatively childhood SAD and later psychopathology may be triggered be a common vulnerability.

21.4. Selective Mutism

21.4.1. DSM-5 Criteria

Diagnostic criteria for SM are the same in the DSM-IV-TR and DSM-5 (2, 3). Criteria state that children diagnosed with SM do not speak in certain situations (e.g., school), even though they have demonstrated the ability to speak in other environments (e.g., home). This symptom must be present for at least 1 month, cause impairment, and not be due to a lack of knowledge of the required language. The failure to speak cannot be due to a communication disorder or another psychiatric illness.

21.4.2. Clinical Presentation

Youths with SM commonly present with other manifestations of anxiety, including, but not limited to: being shy or socially isolated, being worried about embarrassing oneself, seeking reassurance or physical comfort, and compulsive tendencies. Behavioral difficulties (tantrums, oppositionality, defiance) are common as well. Youths often receive additional anxiety diagnoses, and social anxiety disorder is most frequent. Fewer than 1% of individuals seen in mental health clinics receive a diagnosis of SM and it is slightly more common in females than males.

21.4.3. Course and Outcome

While children with SM commonly do not receive clinical attention until they enter school, the onset of the difficulties often begins before age 5. The course of SM is variable; for some, the disturbance may resolve within months, whereas for others the symptoms and associated anxiety can become chronic.

Black and Uhde (63) suggested that SM is a subtype of social anxiety disorder, not a separate diagnostic category. Their sample of 30 children (21 females, 9 males) had a mean age of 8.4 years and mean age of symptom onset at 2.7 years. Ninety-seven percent of participants met criteria for social anxiety disorder, avoidant disorder (DSM-III diagnosis), or both. It was common for first degree relatives to have a history of social anxiety disorder, avoidant disorder, or SM. Subjects were assessed regarding their history of trauma, medical illness, and other possible precipitating factors, but no causal or temporal associations were identified. In contrast, a study by Manassis and colleagues (64) suggested that children with SM can be distinguished from those with social anxiety disorder. Twenty-three subjects participated (14 with SM and 9 with social anxiety disorder). The sample included 14 females and 9 males. The mean age for the SM group was 10.1 years while the social anxiety disorder group was slightly older (11.3 years). Results of questionnaires revealed trends for the social anxiety disorder group to show greater separation anxiety, more physiological anxiety, greater social anxiety, and greater fear of negative evaluation. Scores on cognitive and academic measures were within the normal range and did not differ between groups. The SM group scored significantly lower than the social anxiety disorder group on discrimination of speech sounds and there was a trend for the former to have poorer performance on a test of receptive vocabulary. While six children in the SM group fell in the clinically significant range on at least one language ability measure, none in the social anxiety disorder group fell in this range. Longitudinal studies are necessary to determine whether language difficulties contribute to the development of anxiety or if chronic anxiety and mutism lead to language deficits (64).

Bergman and colleagues (65) developed the Selective Mutism Questionnaire (SMQ) to assess the frequency with which a child speaks in different settings. The factor structure and internal validity of the measure were assessed based on responses from parents of 589 children. Parents were recruited via websites dedicated to SM and 47% of respondents indicated that a psychiatrist or psychologist had diagnosed their child with SM. The sample was 68% female. The mean age of the children was 6.3 years and the mean age of symptom onset was 3.1 years. The SMQ assesses three different environments in which the child speaks: School, Home/Family, and Public/Social. Parents rated their children as least likely to speak in public and most likely to speak at home. A limitation of this study is that it is unclear if all children had SM because formal diagnostic evaluations were not administered.

To further evaluate the psychometric properties of the SMQ, 48 children with SM and 18 with other anxiety disorders were administered the instrument (65). The mean age of participants and the mean age of symptom onset were similar to the 589 children who participated in the study of the factor structure and internal validity of the instrument. Convergent validity was demonstrated by significant correlations between scores on the SMQ and scores on the Social Anxiety Scale for Children—Revised (66) and on the Social Anxiety Scale of the Multidimensional Anxiety Scale for Children—Parent Report (67).

21.5. Fears and Specific Phobias

The majority of children and adolescents experience fears throughout development (68). Childhood fears vary in duration, frequency, and severity. However, fears are typically mild, age-specific, and quickly dissipate. They are often adaptive to situations (e.g., fear of strangers) and do not involve intense or persistent reactions. Fears typically follow a predictable course during childhood and are mediated by children's daily experiences and cognitive capacities (69). During infancy, children are fearful of stimuli in their immediate environment. As children mature, their fears are more likely to include anticipatory events, as well as imaginary or abstract stimuli.

21.5.1. DSM-5 Criteria

In contrast to normal childhood fears, phobias are diagnosed when the individual exhibits marked and persistent fear that is considered excessive or unreasonable (2). However, children may not view these fears as excessive or unreasonable. The fear response is triggered by the presence or anticipation of a specific object or situation. There are five general types of phobias: animal (e.g., snakes, spiders, dogs), natural environment (e.g., storms), blood–injection–injury (e.g., needles for blood drawing), situational (e.g., flying), and others (e.g., loud noises, costumed characters). Exposure to the feared stimulus immediately results in an anxiety response and the feared stimulus is avoided or endured with intense anxiety. Children often express their fears by crying, having tantrums, clinging to adults, or freezing, which is different than the adults' typical response of a panic attack. To be diagnosed with a specific phobia, children must demonstrate these symptoms for at least 6 months and the symptoms must interfere with daily functioning and/or relationships. The diagnostic criteria for specific phobia did not change from the DSM-IV-TR to the DSM-5.

21.5.2. Clinical Presentation

There appear to be differences in the prevalence rates of specific phobia found in children from community versus clinical samples. The prevalence of specific phobia in community samples of children and adolescents ranges from 2.6 to 9.1%, with an average of approximately 5% across studies (68, 70). The prevalence of specific phobia in clinical samples of children and adolescents is estimated to be about 15% (71); however, this may be an overestimate of actual occurrence due to a failure to document impairment caused by symptoms. The most common phobia types across various samples are the animal and natural environment types (72).

There was a nearly 8% 1-year prevalence rate of specific phobia found in an Asian community sample of 2,673 children and adolescents who ranged in age from 6 to 17 years (70). Several studies show that youth with specific phobia are more likely to be younger and female compared with participants who do not meet criteria for a specific phobia (70, 73). However, when examining the different types of specific phobias, there was no gender difference in the blood–injection–injury phobia type and children with animal phobias had a higher socioeconomic status (70). Kim and colleagues (70) found that approximately 57% of participants endorsed multiple types of specific phobias.

Each specific phobia type seems to have a unique manifestation of physical and cognitive symptoms (74, 75). The individual's response to exposure to the feared stimulus differs based on the type of phobia. Exposure in animal phobia results in sympathetic activation (i.e., tachycardia) which elicits heightened arousal, whereas exposure in blood–injection–injury phobia results in parasympathetic activation (i.e., bradycardia) which elicits dizziness and possible fainting. In addition, maladaptive cognitions (i.e., "I am going crazy") and misinterpretations of physical symptoms are more pronounced in environmental and situational phobias. Comorbidity is less common in children and adolescents with specific phobia compared with those with other anxiety disorders (76). A community sample of youth with specific phobia showed that 28% endorsed at least one other psychiatric diagnosis (70). The most common comorbid disorders were another anxiety disorder, ADHD, and ODD. The different subtypes of specific phobia may have unique patterns of comorbidity. Kim and colleagues (70) found that an animal phobia was associated with an anxiety disorder and ODD, natural environment phobia was associated with an anxiety disorder only, and blood–injection–injury phobia was associated with ADHD. In a clinical sample of youth with specific phobias, approximately 33% endorsed at least one other comorbid disorder (72). Of the youth with specific phobias, 33% were also diagnosed with GAD, 23% with social anxiety disorder, 19% with SAD, and 16% with ADHD.

21.5.3. Course and Outcome

Childhood phobias may develop following a frightening experience, after observing a terrifying reaction in others, or when learning about fears (77). However, there are childhood phobias that have no identifiable cause and are reported to always have been present in the child. Studies suggest that there is a modest degree of continuity of phobias in children and adolescents across intervals that range from 2 to 5 years. Approximately 20–40% of children diagnosed with phobias continue to demonstrate phobias at a later point in time (78). Avoidance behavior likely serves to maintain the phobias. This behavior minimizes the individual's contact with the feared stimulus and prevents the individual from learning that exposure to the feared stimulus is not associated with the feared catastrophic outcome (79). A longitudinal twin study in which participants were assessed four times between 8 and 20 years of age showed that the mean fear levels of participants decreased with age (80).

21.6. Social Anxiety Disorder

Prior to the DSM-IV, children and adolescents who feared and avoided engaging in contact with unfamiliar people were typically diagnosed with avoidant disorder of childhood or adolescence. This diagnosis was not included in the DSM-IV, and these children and adolescents were diagnosed with social phobia in DSM-IV which is referred to as social anxiety disorder in DSM-5.

21.6.1. DSM-5 Criteria

The DSM-5 uses the term social anxiety disorder rather than social phobia, which was used in the DSM-IV-TR. The criteria for social anxiety disorder and social phobia are the same in both diagnostic manuals. Social phobia and social anxiety disorder are characterized by marked and persistent anxiety regarding social or performance situations that is due to fears that the individual will act in a way that is embarrassing or humiliating (2, 3). For example, children with social anxiety disorder often worry that their peers will laugh at them if they say the wrong thing when called on in class. The feared situations are avoided or endured with intense distress, and exposure to the feared situations almost always produces anxiety. There are differences in the DSM-5 criteria for social anxiety disorder in children compared with adults. Children with social anxiety disorder must demonstrate anxiety in settings with peers as well as with adults, and anxiety symptoms may take the form of crying, tantrums, freezing, clinging, or failing to speak in social situations. Social anxiety disorder symptoms must cause interference in the functioning of the child or adolescent. In persons younger than 18 years of age, duration of symptoms must be at least 6 months. The majority of children with social anxiety disorder have the generalized type (81, 82) that is characterized by fear of most social or performance situations. The DSM-5 indicates that it should be specified if the individual only demonstrates social anxiety disorder when required to speak or perform in public.

21.6.2. Clinical Presentation

The mean age of onset of childhood social anxiety disorder in a clinical setting is reported to range from 11.3 years (47) to 12.3 years (83). Social anxiety disorder is diagnosed more frequently in females compared with males (84). However, there are no gender differences in the presentation of social anxiety disorder (81, 85). Studies have been conducted to examine the clinical presentation of children and adolescents diagnosed with social anxiety disorder. Beidel and colleagues (81) evaluated a clinic sample of 50 children with social anxiety disorder (ages 7–13 years). These children manifested poor social skills and used maladaptive coping behaviors (e.g., avoidance) in social or performance situations. Children with social anxiety disorder also had difficulty with peer relationships; 75% reported few or no friends and 50% did not participate in extracurricular activities. Furthermore, 50% disliked school and 10% refused to attend school regularly.

Kramer and colleagues (86) compared children (7–12 years) with social anxiety disorder ($n=41$) and healthy controls ($n=40$) during the Trier Social Stress Test for Children (87). The social anxiety disorder group reported higher subjective anxiety across the entire test. Additionally, their anxiety increased and then decreased more quickly than that of the control group. The social anxiety disorder group also had an elevated heart rate across the duration of the test in comparison with the controls. Increases in salivary alpha-amylase in response to the task were demonstrated by both groups. The groups also experienced similar changes with respect to salivary cortisol. The authors suggest that youths with social anxiety disorder may experience autonomic hyperactivity separate from the hypothalamic–pituitary–adrenal system. In a nonclinical sample of 7–11 year olds, children with social anxiety disorder ($n=45$) were compared with anxious children without social anxiety disorder ($n=56$) in order to identify characteristics unique to social anxiety (82). Children with social anxiety disorder feared and avoided a significantly greater number of social situations than anxious children without this disorder. In addition, significantly more children with social anxiety disorder compared with anxious children without social anxiety disorder described difficulty making friends (49% versus 24%, respectively) and significantly more preferred to be alone rather than with peers (24% versus 7%, respectively). Per teacher report, children with greater severity of social anxiety disorder symptoms exhibited significantly poorer social skills, poorer leadership skills, increased attention difficulties, and greater learning problems.

Alfano and colleagues (88) evaluated the cognitions of 50 youths with social anxiety disorder and 30 healthy controls. Youths in the social anxiety disorder group rated themselves as more anxious than the control group during a role-play task and while reading out loud. The social anxiety group had lower expectations of their performance on the role-play than the control group. Furthermore, the social anxiety disorder group believed they would have difficulty hiding their anxiety and they expected to be judged negatively by their peers. Independent observers rated the children with social anxiety disorder as significantly more anxious and less effective than the controls during the tasks. During the role-play, the social anxiety disorder group had significantly more negative self-talk comments regarding performance (e.g., "I can't do this") than the healthy controls. Poorer expectations expressed by those with social anxiety disorder were supported by blind observers who rated these children as more

anxious and less effective compared with controls. Based on these findings, negative beliefs about performance are an integral concern of youth with social anxiety disorder and high anxiety during tasks likely interferes with effective social functioning.

Children with social anxiety disorder have negative cognitions in social situations, viewing themselves as less socially adept than their peers (89). They expect poor outcomes in social settings, and in fact, fare less well in social interactions. Socially anxious children report negative peer interactions (85). Children with social anxiety disorder compared with nonanxious children are more likely to be ignored, excluded, and rejected by classmates (89).

Children and adolescents with social anxiety disorder frequently have a comorbid disorder. Beidel and colleagues (81) found that 60% of children (7–13 years) with social anxiety disorder met criteria for another diagnosis. Thirty-six percent had another anxiety disorder, 10% had ADHD, 8% had SM, and 6% had an affective disorder.

21.6.3. Course and Outcome

Social anxiety disorder often begins during preadolescence and typically has a chronic course throughout adulthood (90, 91). A diagnosis of social anxiety disorder may be associated with social, educational, and occupational impairments. Common negative outcomes of this disorder in adults include social isolation, difficulty holding jobs, depression, drug abuse, and suicide attempts (90, 92–95). Due to avoidance of performance and social situations and other impairments related to social anxiety disorder, many individuals fail to graduate high school (96). In a retrospective study of adults with anxiety disorders ($N=201$), half of the participants reported that they disliked school with the most common reasons being difficulty speaking in front of the class (28%) and feeling nervous at school (25%) (97). Also, the study revealed that half of the sample dropped out of school, with the most common reason being feeling nervous at school. The researchers concluded that the main reason for dropping out of school was due to social anxiety disorder symptoms.

21.7. Generalized Anxiety Disorder

Prior to the DSM-III-R, the diagnosis of GAD required that the individual be at least 18 years of age. Children and adolescents who endorsed excessive worry would have been considered for a diagnosis of OAD. OAD was eliminated in the DSM-IV and the age requirement was deleted from the criteria for GAD, which allowed children and adolescents to be diagnosed with GAD.

21.7.1. DSM-5 Criteria

DSM-5 criteria for GAD are consistent with the criteria stated in the DSM-IV-TR. The primary feature of GAD is a pattern of excessive anxiety and worry about numerous topics that occurs for more days than not for at least 6 months (2). The worry is difficult to control and there is at least one symptom associated with the worry symptom (three associated symptoms are required for adults). These symptoms include restlessness, fatigue, difficulty concentrating, irritability, muscle aches or tension, and sleep difficulties. The anxiety or associated symptoms cause significant impairment or distress in important areas of functioning.

21.7.2. Clinical Presentation

Prevalence estimates of GAD in a general population (15–54 years old) are approximately 1.6% current and 5.1% lifetime, with approximately twice the occurrence in females compared with males (98). Pina and colleagues (99) examined which worry domain was most predictive of a diagnosis of GAD in a clinic sample of 111 children and adolescents (6–17 years old). Results showed that uncontrollable excessive anxiety about one's own health was most predictive of the youth meeting diagnostic criteria for GAD compared with other domains of uncontrollable anxiety (e.g., perfectionism, school, health of others).

Benjamin and colleagues (100) investigated the number of worries and/or physiological symptoms and the types of worries that differentiate children with GAD from those with SAD and/or social anxiety disorder and from youths with no anxiety diagnosis. Parent report indicated that youths with GAD had significantly more worries and physiological complaints compared with youths in the SAD and/or social anxiety disorder and no anxiety diagnosis groups. However, child report of number of worries and physiological complaints was not significantly different between the groups. Based on parent report, three worries and four physiological symptoms were the optimal numbers to distinguish youths with GAD from the other two groups. Parental report of worries about school, performance, social situations, perfectionism, health of others, and child's health distinguished youths with GAD from those with no anxiety disorder. Worries about little things, health of self and others, and world affairs distinguished GAD from SAD and/or social anxiety disorder. Child-reported worry about school differentiated the GAD group from the SAD and/or social anxiety disorder group.

Parent report of all six physiological symptoms (i.e., unable to relax, tires easily, trouble concentrating, irritability, muscle aches, and difficulty sleeping) differentiated those with GAD from those with no anxiety diagnosis. However, none of the physiological symptoms distinguished GAD from SAD and/or social anxiety disorder. The authors suggest that the later finding is related to the high prevalence of somatic complaints in youths with any anxiety disorder. Based on parent report, GAD can be distinguished from SAD and/or social anxiety disorder using the number and types of worries. Consequently, the data support GAD as a distinct diagnosis. Regarding practical application of these findings, it was suggested that interviews with parents begin by assessing worries related to health and world affairs, while interviews with children and adolescents begin with discussing worries about school.

Masi and colleagues (101, 102) examined the symptom presentation in clinical samples of children and adolescents diagnosed with GAD. Masi and colleagues (101) interviewed 58 subjects ranging from 7 to 18 years of age and found that the majority of participants endorsed feelings of tension (98%), apprehensive expectations (95%), need for reassurance (83%), irritability (81%), negative self-image (74%), and physical complaints (72%). There were differences across age groups when comparing children and adolescents, with children reporting a higher need for reassurance and adolescents reporting more frequent brooding (101). A subsequent study did not find differences in GAD symptom presentation across age groups (102). Significant differences in symptom presentation were not found between genders (101, 102).

Children and adolescents with GAD worry about a variety of events and situations. Research shows that their worry is most often related to school performance (103). Other common GAD worries during childhood are fears of social situations, natural phenomenon, and keeping a schedule (i.e., not arriving late). During adolescence, worries are more commonly characterized by continuous self-doubt, sensitivity to criticism, and need for constant reassurance (103). Both children and adolescents seem to worry frequently about social acceptability, personal competence, and expectations about the future (101).

Other anxiety disorders and mood disorders are frequently comorbid with GAD in children and adolescents. A study of 157 children and adolescents with GAD showed that 93% of participants endorsed a comorbid disorder (102). Typically, mood disorders were determined to follow the onset of GAD, with depressive disorders being the most frequent comorbid disorder. A possible reason for the high comorbidity rates of GAD with affective disorders may be due to the symptoms that are common across disorders, such as impaired concentration and sleep difficulties (104). In addition to comorbid internalizing disorders (e.g., anxiety and depressive disorders), 21% of the participants met criteria for a comorbid externalizing disorder (ADHD, ODD, conduct disorder) (102).

Since there is a high rate of comorbidity of depressive disorders in children and adolescents with GAD, studies have compared children and adolescents with GAD to children and adolescents with GAD plus depression. One study found that individuals with comorbid depression endorsed significantly greater impairment (58). Specifically, participants with GAD and a comorbid depressive disorder endorsed a greater number of anxiety symptoms and greater irritability.

21.7.3. Course and Outcome

Age of onset of GAD appears to have a bimodal distribution with an early onset occurring during childhood and adolescence and a later onset occurring during adulthood (98). The prevalence rate of GAD tends to increase with age from childhood to adulthood (101). The course of childhood GAD is typically chronic with fluctuations in severity of symptoms. A comorbid diagnosis of depression is indicative of a poorer prognosis with a longer duration and more severe symptoms (101). In addition, children with high levels of GAD symptomatology are more likely to begin drinking alcohol at an earlier age compared with other children (105).

21.8. Obsessive-Compulsive Disorder

Minor obsessions and compulsions, as well as normal developmental rituals (e.g., bedtime routines), commonly occur in young children and are not considered pathologic because they are not associated with distress or dysfunction (106). The intrusive, and sometimes bizarre, nature of obsessional thoughts and the embarrassment associated with rituals lead children with OCD to minimize or be secretive about their symptoms. Children who minimize their symptoms or experience mild symptoms are often difficult to identify in the general population.

21.8.1. DSM-5 Criteria

Although OCD is placed in a different section of the DSM-5 (Obsessive-Compulsive and Related Disorders) compared with in the DSM-IV-TR, the diagnostic criteria primarily remain the same. In the DSM-5 (2), either obsessions or compulsions with the associated characteristics are needed to qualify for a diagnosis of OCD. Obsessive ideas recur and persist and are

experienced as intrusive and senseless and cause excessive anxiety or distress. Compulsions are repetitive behaviors or mental acts that an individual feels compelled to perform. To meet criteria for OCD, the individual must experience distress, spend more than 1 h per day engaged in obsessions or compulsions, or experience functional impairment in his/her life due to OCD.

21.8.2. Clinical Presentation

Heyman and colleagues (107) studied the prevalence rates of OCD in a community sample of 10,438 children and adolescents (age range: 5–15 years). Results indicated an overall prevalence of 0.25% with an increase in prevalence correlated with an increase in age. Prevalence rates of OCD for the specified ages were as follows: 5–7 years, 0.026%; 8–10 years, 0.14%; 11–12 years, 0.21%; 13–15 years, 0.63%. Prevalence rates have been found to be higher (2–4%) in samples of adolescents who range up to 18 years of age (108–110). In children, the male to female ratio is around 3:2 (111), with the gender ratio approximately equal in adolescents (112).

Symptoms suggestive of OCD include excessive cleaning rituals (e.g., hand washing), counting rituals, and ordering behaviors. Long periods of time spent on homework, including frequent erasures, redoing parts of assignments multiple times, and rereading, can be indicative of OCD (113). Wearing the same outfit daily, using towels only once, washing clothes frequently, and using excessive amounts of toilet paper are clues that a child may have contamination obsessions due to OCD (113). Other common OCD symptoms include excessive need for reassurance, preoccupation with germs, hoarding of useless objects, and requesting family members to repeat phrases or engage in other repetitive actions. Parents may become aware of the problem when children become dysfunctional due to the frequency and complexity of the rituals (e.g., children who are late to school due to repeated hand washing and checking behaviors before leaving the house).

OCD characterized by both obsessions and compulsions is the most common presentation in youth (114, 115), and it is rare that children experience obsessions without compulsions (115). In a study of 70 consecutive cases of OCD in children and adolescents, the most commonly reported obsessions focused on dirt or germs, danger to self or relatives, and symmetry (115). The most frequent compulsions included excessive washing (e.g., hand washing, showering, tooth brushing) in 85%, repeating rituals in 51%, and checking in 46%. In a study of 77 children and adolescents with OCD [including 22 with pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS)], the most common obsessions were contamination and aggression, and the most common compulsions were checking, washing/cleaning, and repeating (116). Multiple current obsessions and compulsions were reported by 85% of youth with OCD (116).

A subgroup of children with OCD and/or tic disorders has been characterized as having PANDAS. PANDAS is defined by the following criteria: (1) presence of OCD and/or tic disorder; (2) prepubertal onset; (3) sudden, dramatic onset with acute, episodic exacerbations of symptoms; (4) temporal association between streptococcal infections and symptom onset and exacerbation; (5) neurological symptoms (e.g., hyperactivity, choreiform movements) (117). Diagnosing of PANDAS can be challenging due to the difficulty in documenting the temporal relation between streptococcal infections and onset or worsening of neuropsychiatric symptoms (118). In a study comparing children with PANDAS ($n=21$) and non-PANDAS OCD ($n=18$), those with PANDAS were significantly more likely to manifest the following symptoms during their initial episode of neuropsychiatric symptoms: separation anxiety, urinary urgency, symptoms of ADHD, mood swings, deterioration of handwriting, and decline in school performance (118). Although streptococcal infections are presumed to be involved in the etiological pathway leading to OCD in children with PANDAS, the mechanism by which this occurs is yet to be clearly delineated. Circulating autoimmune antibodies directed against neuronal structures (e.g., basal ganglia in the brain) have been hypothesized as playing a role in the pathogenesis of PANDAS (119).

Comorbidity is frequently documented in children and adolescents with OCD. Heyman and colleagues (107) found 76% of the children and adolescents with OCD had at least one comorbid diagnosis. The comorbidity rate of tic disorders in children with OCD ranges from 21% (112) to 28% (120).

21.8.3. Course and Outcome

There is a bimodal pattern to age of onset for OCD, with one peak in childhood and another in adulthood. The mean age of onset in children ranges from 7.5 to 12.5 years (M = 10.3) (112), whereas the mean age of onset in adults is 21 years (121). Boys typically have an earlier age of onset (prepubertal) than girls (peripubertal). Early onset OCD is associated with male predominance, comorbid tic disorder, comorbid ADHD, and family history of OCD (112, 122). Many children with OCD have a gradual shift to new symptoms over time. Most children report that their symptoms have periods of exacerbations and remissions.

A meta-analysis of 16 pediatric OCD samples ($N=521$) with follow-up periods ranging from 1 to 15.6 years (M = 5.7 years) demonstrated that rates of persistence of OCD were lower than previously believed (123). Mean percentage with persistence of an OCD diagnosis was 41% in the pooled sample. Mean percentage with persistence of any OCD symptoms was 61%. Predictors of persistence of illness were early age of onset, longer duration of illness, and inpatient status.

21.9. Panic Disorder

The first report of panic symptoms in adolescents was published in 1984 (124), and since that time studies have been conducted which indicate that symptom presentation is similar across ages and panic disorder can be diagnosed in children and adolescents.

21.9.1. DSM-5 Criteria

Panic attack is a sudden surge of intense fear and discomfort that peaks within minutes and is associated with at least four symptoms (e.g., accelerated heart rate, sweating, shaking, shortness of breath, fear of losing control). In addition to having these recurrent and unexpected panic attacks, the individual has persistent concern about experiencing another attack, worries about the consequences of the future attacks, or makes significant changes in behavior due to fear of having another attack.

21.9.2. Clinical Presentation

Panic disorder is rare in children. Less than 1% of children and 2–4% of adolescents meet criteria for panic disorder (125). Panic attacks are found to occur in children and adolescents at a higher rate than panic disorder. Essau and colleagues (126) interviewed 1,035 adolescents (12–17 years old) from a nonclinical sample (i.e., individuals within the community, rather than individuals seeking services in a clinic), and found a lifetime prevalence rate of 0.5% for panic disorder and an 18% prevalence rate for having at least one panic attack. The mean age of onset of panic disorder is after puberty (127), typically during early to middle adulthood (128).

Studies have examined the description of panic attacks in children and adolescents, and have found differences across the developmental lifespan (57, 129, 130). Younger children report palpitations, shortness of breath, sweating, faintness, and weakness as the most common symptoms during a panic attack. In contrast, adolescents report chest pain, trembling, headache, and dizziness as the most frequent symptoms. Diler and colleagues (131) found the most common panic symptoms in adolescents with panic disorder to be palpitations, chest pains, feeling faint, and trembling. The occurrence of cognitive symptoms associated with panic attacks appears to be related to age and tends to occur after the development of physical symptoms (57). Children and early adolescents typically report fear of dying as the earliest cognitive symptom. Later onset cognitive symptoms are usually a fear of going crazy or losing control and thoughts regarding depersonalization–derealization (e.g., do not know who I am or where I am) (57). Risk factors for developing panic disorder are a parental history of panic disorder, negative affect in childhood, and a history of chronic illness in a parent (132). It has been suggested that watching a parent suffer with a chronic illness can be associated with developing a learned hypersensitivity to physiological symptoms (132).

High rates of comorbidity have been documented in children and adolescents with panic disorder. Masi and colleagues (133) found that all participants diagnosed with panic disorder had a comorbid anxiety disorder and 43% had a comorbid depressive disorder. The comorbidity rates for specific anxiety disorders showed that 74% met criteria for GAD, 56% for agoraphobia, 56% for specific phobias, and 30% for OCD. In addition, 73% of the children and adolescents currently met criteria for or had a history of SAD. Diler et al. (131) found that 48% of 14- to 24-year-olds who had experienced a panic attack had a comorbid diagnosis.

21.9.3. Course and Outcome

Researchers have expressed doubt about whether panic disorder occurs in young children due to their inability to experience the cognitive symptoms associated with the disorder (133). Children are not able to hold internal attributions of causality, which is necessary for the cognitive symptoms of panic disorder. These cognitive capabilities do not exist until abstract thinking is developed during adolescence. Children and younger adolescents typically focus on cues that are present in the external environment, whereas older adolescents attribute symptoms to internal sensations.

The incidence of first panic attacks seems to increase during adolescence, and research has shown that there may be biological factors (e.g., onset of puberty) related to this increase in occurrence. A study examined the influence of age and pubertal stage on panic attacks in 754 sixth and seventh-grade females to improve understanding of panic attacks during adolescence (134). The participants completed a structured clinical interview regarding history of panic episodes and a self-assessment of Tanner stage of pubertal development. Results indicated that 5.3% of the females endorsed a history of at least one panic attack. Higher Tanner stage was positively correlated with higher rate of panic attacks after controlling for age.

Research consistently shows that anxiety sensitivity, a tendency to respond in a fearful manner to anxiety symptoms, is specifically related to the onset of panic attacks (135, 136). Individuals with panic disorder commonly exhibit interoceptive sensitivity which is sensitivity to physical sensations, especially from the cardiac system (137). An increase in sensitivity to bodily sensations is believed to precede impaired perceptions of bodily sensations and a bias to catastrophic thinking that occurs with panic (138). Conditional anxiety responses to interoceptive stimuli appear to maintain the anxiety symptoms (139).

Children and adolescents who experience panic attacks may have a chronic course throughout adulthood, and there is a substantial potential for additional psychopathology (i.e., major depression, bipolar disorder, anxiety disorders) following panic attacks (57, 94, 140). However, there are some individuals who experience panic attacks and do not develop psychopathology (127). A prospective study with 2,246 high school students examined factors that contribute to differential trajectories following initial panic attacks (141). Anxiety sensitivity, negative affect, and childhood behavioral inhibition significantly predicted the severity of panic attacks and the development of internalizing symptoms following the initial panic attack. In addition, panic attack severity predicted the development of agoraphobia and depression. Adolescents who reported panic attacks endorsed significantly lower levels of support from family and higher levels of stress in the home compared with adolescents who did not experience panic attacks (142).

Adolescents and young adults with panic disorder are at higher risk of suicidal behavior and attempts after controlling for comorbid disorders and stressors (143, 144). It has been shown that early onset panic disorder (prior to 18 years of age) compared with later onset panic disorder (18 years and older) is associated with greater difficulties in adulthood, which include alcohol abuse, suicidal thoughts and attempts, and increased use of emergency departments (145).

21.10. Treatment

It is critical that a comprehensive diagnostic assessment, including clinical interviews, is completed with the child and parents to obtain a complete understanding of the clinical presentation of the anxiety disorder. In addition, it is often beneficial to gather information from the school, previous or current treatment providers, and the pediatrician. There are several medical conditions in children that may present with anxiety-like symptoms, including hyperthyroidism and caffeinism (146). In addition, the following medications may be associated with anxiety symptoms as side effects: antiasthmatics, sympathomimetics, steroids, selective serotonin reuptake inhibitors (SSRIs), and typical and atypical antipsychotics (146). Therefore, a careful review of systems, review of current medications, and a pediatric examination are important. In some cases, laboratory tests including thyroid studies and a drug screen will be indicated. Following a complete assessment, a multimodal treatment approach should consider psychosocial and psychopharmacology components (146).

21.10.1. Cognitive-Behavioral Therapy

Although there are numerous psychosocial approaches used to treat childhood anxiety disorders (e.g., cognitive-behavioral therapy [CBT], psychodynamic psychotherapy, play therapy, supportive therapy), CBT is the only approach whose efficacy is supported by data from randomized controlled studies (147). Velting and colleagues (148) identified the following six essential components of CBT in the treatment of childhood anxiety disorders: psychoeducation, somatic management, cognitive restructuring, problem solving, exposure, and relapse prevention. Numerous cognitive-behavioral treatment programs that include various combinations of these components have been developed and evaluated for use in individual, group, and family therapy settings. Research has consistently demonstrated that both individual and group CBT are superior to a waiting-list control condition (i.e., no treatment) in treating children with anxiety disorders (i.e., (149, 150)).

Kendall (150) conducted the first randomized controlled study to assess the outcome of a manual-based CBT intervention referred to as the *Coping Cat* (151, 152). Forty-seven participants, ages 9–13 years old, with primary diagnoses of OAD, SAD, or avoidant disorder (social anxiety disorder) were assigned to a treatment or wait-list control condition. Results showed that children who participated in the treatment condition performed better on the majority of outcome measures, demonstrating fewer symptoms of anxiety and depression compared with children in the wait-list condition. Sixty-four percent of the children who participated in the CBT intervention no longer met criteria for an anxiety disorder, whereas only 5% of wait-list controls no longer met criteria following the waiting period. Follow-up assessments at 3 years (153) and 7.5 years (154) indicated maintenance and enhancement of these treatment gains over time.

Further research has been conducted to compare the outcome of individual CBT, group CBT, and wait-list control conditions when treating childhood anxiety disorders. Flannery-Schroeder and Kendall (149) used the *Coping Cat* intervention program to examine these group differences in children ages 8–14 years old ($N = 37$) with a primary diagnosis of GAD, SAD, or social anxiety disorder. Individual CBT and group CBT were equally effective and both were more effective than the wait-list control.

Following treatment, 73% of children who participated in individual CBT and 50% of children who participated in group CBT no longer met diagnostic criteria for their primary anxiety disorder. In contrast, only 8% of the children on the waitlist no longer met criteria following the waiting period. Flannery-Schroeder and colleagues (155) found that these children continued to demonstrate improvements in anxiety at 1-year follow-up. Specifically, 81% of the children who participated in individual CBT and 77% who participated in group CBT no longer met criteria for their primary anxiety disorder. CBT alone or in combination with an SSRI is effective in treating pediatric OCD (156). Please refer to Sect. 21.10.3.

A series of studies has demonstrated the efficacy of family CBT conducted in a group format (i.e., (157–159)). Silverman and colleagues (159) completed a randomized clinical study ($N=56$) to compare the outcomes of group CBT with separate, concurrent groups for parents and children and wait-list control. Results indicated that 64% of the children who received group CBT no longer met diagnostic criteria for their primary anxiety diagnosis, compared with only 13% in the wait-list control group. Barrett and Turner (157) developed and evaluated the FRIENDS program, which is a 10-session family-based group CBT intervention aimed to enhance skills and competencies to manage anxiety-provoking situations. The efficacy of FRIENDS was evaluated with 71 children (ages 6–10 years) who had a primary diagnosis of SAD, GAD, or social anxiety disorder (158). The results indicated that 69% of children who completed FRIENDS no longer had a diagnosis, compared with 6% of children on the wait-list.

Studies have also been completed to evaluate the role of parental involvement in the treatment of childhood anxiety disorders (i.e., (160, 161)). Barrett and colleagues (160) compared anxious children who participated in a CBT intervention that included a family therapy component compared with children who participated in CBT that did not include parental involvement. Results showed that the effects of CBT with a family component were greater than CBT alone immediately posttreatment and at 1-year posttreatment; however, these differences were not present at 6 years posttreatment (162). Another study compared the effects of CBT alone, CBT plus parent training, and wait-list control, and found that both CBT groups were superior to wait-list control, but there was no additional benefit of parent training (161). Cobham and colleagues (163) examined the parent component further and results indicated that a parental anxiety management component increased the efficacy of CBT only for children with at least one anxious parent.

In addition to these clinic-based studies, several school-based studies have been conducted as preventative and early intervention efforts using CBT-based procedures (i.e., (164, 165)). Dadds and colleagues (165) screened 1,786 children from Australia in third through sixth grades and identified 128 who were anxious. These children were then assigned to a 10-week school-based child and parent-focused CBT intervention using *The Coping Koala: Prevention Manual* or a monitoring-only group. At 6-month follow-up posttreatment, results showed that the participants from the child and parent-focused group endorsed a lower rate of diagnosable disorders compared with the monitoring only group (16% versus 54%). Bernstein and colleagues (164) expanded on the research conducted by Dadds et al. by implementing the FRIENDS program in elementary schools in the United States. Sixty-one children (ages 7–11 years) across three elementary schools were identified as anxious and randomized by school to group CBT for children, group CBT for children plus concurrent parent training group, or no-treatment control. Findings showed that children who participated in either CBT treatment condition had a significant decrease in anxiety and associated impairment at posttreatment compared with children in the no-treatment control group. In addition, some outcome measures showed significantly greater improvement in child anxiety for group CBT plus parent training compared with group CBT alone.

21.10.2. Psychopharmacology

Psychopharmacological treatment is considered as part of a multimodal treatment plan if the level of anxiety symptomatology is severe and there is substantial functional impairment due to the symptoms (146). Other factors that support the use of medications include partial response to unimodal treatment (e.g., anxiety interferes with child's participation in CBT), presence of comorbidity (e.g., major depression), and older age of the child. SSRIs are the first-choice class of medication for targeting anxiety symptoms in youth. There are a number of randomized, double-blind, placebo-controlled studies that demonstrate the efficacy of SSRIs in decreasing anxiety symptoms and support their short-term safety in children and adolescents with anxiety disorders (156, 166–170).

There are physical and psychiatric side effects of SSRIs (171). Common physical side effects include stomachaches, headaches, and insomnia. Psychiatric side effects include motor activation which is one of the most common of all SSRI side effects in children. Other psychiatric side effects are disinhibition, agitation, increase in anxiety, and suicidal ideation/behavior (please refer to Sect. 21.10.2.6).

21.10.2.1. Selective Serotonin Reuptake Inhibitors

A multicenter study examined 8 weeks of fluvoxamine versus placebo for children and adolescents ages 6–17 years with SAD, GAD, and/or social anxiety disorder ($N=128$) (167). Dosage of fluvoxamine was 50–250 mg/day for children and up to 300 mg/day for adolescents. Fluvoxamine was significantly better than placebo in decreasing anxiety symptoms on a clinician rating scale at

posttreatment. In addition, the CGI Improvement scale demonstrated that significantly more participants in the fluvoxamine condition were rated at or above "improved" compared with the placebo group (76% versus 29%, respectively). Overall, medication was well tolerated with only 8% of children on fluvoxamine and 2% on placebo discontinuing due to side effects. Significantly more participants on active medication reported stomachaches compared with those on placebo, and there was a trend toward increased likelihood of motor activation in the fluvoxamine group.

In another pharmacological treatment study, youths ages 5–17 years with a primary diagnosis of GAD ($N=22$) were treated with sertraline (maximum dosage of 50 mg/day) or placebo for 9 weeks (168). From week 4 to posttreatment, the sertraline group showed significantly more improvement on a clinician rating scale of anxiety compared with the placebo group. Self-report measures also showed significantly greater decreases in anxiety for the children on active medication compared with those on placebo. There were no significant differences between groups with respect to side effects.

In a third study, children and adolescents (ages 7–17) with SAD, GAD, and/or social anxiety disorder ($N=74$) were treated with fluoxetine (20 mg/day) versus placebo for 12 weeks (166). Sixty-one percent of the children who received fluoxetine versus 35% who received placebo were rated at posttreatment as much or very much improved on the CGI Improvement scale. Stomach discomfort was the only side effect that was significantly more common throughout the study in the fluoxetine group compared with placebo. A large multicenter study investigated 16 weeks of paroxetine (10–50 mg/day) versus placebo in children and adolescents ages 8–17 with social anxiety disorder ($N=322$) (169). At posttreatment, a significantly higher percentage of participants on paroxetine compared with those on placebo had a CGI Improvement score of much or very much improved (78% versus 38%, respectively). Withdrawal from the study due to side effects was uncommon, with 6% of the children on paroxetine leaving the study due to adverse events compared with 1% on placebo. The above studies provide child and adolescent psychiatrists with data that support the efficacy of the SSRIs in treating childhood anxiety disorders.

To our knowledge, no randomized controlled trials of escitalopram in youth with anxiety disorders have been published. However, one open-label trial and a retrospective chart review have been reported. Children and adolescents (ages 10–17) with social anxiety disorder ($N=20$) were treated with 12 weeks of escitalopram in an open-label study (172). Final dose of escitalopram was 2–20 mg/day. Primary outcome measure was the change in CGI Improvement scale from baseline to week 12. Using intent-to-treat analysis, 65% of participants (13 of 20) were much or very much improved on the CGI Improvement scale at posttreatment. A retrospective chart review of escitalopram for the treatment of various anxiety disorders in preschool children ($N=11$), suggested the drug may be efficacious in targeting anxiety (173). The age range of participants was 47–64 months. Escitalopram dose was 2–10 mg/day. On the CGI Improvement scale, three subjects demonstrated moderate to much improvement in anxiety symptoms, three had mild to moderate improvement in post-traumatic stress symptoms, and five exhibited mild to much improvement in OCD symptoms. The most common side effect was behavioral disinhibition, occurring in 45% ($n=5$) of preschoolers. In three of the five participants with behavioral disinhibition, escitalopram was discontinued due to this side effect. The researchers commented that preschoolers may be more prone to side effects, especially behavioral disinhibition (173).

The question of how long to treat an anxiety-disordered child with an SSRI has been addressed. It is recommended that a child be continued on medication for a year after remission of target symptoms (174). Subsequently, during a period of low stress (e.g., summer vacation), it is suggested that the SSRI be tapered and discontinued. However, if the anxiety symptoms recur, it is recommended that the medication be restarted (174).

21.10.2.2. Serotonin Norepinephrine Reuptake Inhibitors

Two large studies evaluated venlafaxine ER, a serotonin norepinephrine reuptake inhibitor (SNRI) for the treatment of anxiety disorders in youth (175, 176). One study enrolled children and adolescents with social anxiety disorder (175) and the other studied youths with GAD (176). The venlafaxine ER dose range in both studies was 37.5–225 mg/day. March and colleagues (175) investigated 16 weeks of venlafaxine ER compared with placebo in 293 children and adolescents aged 8–17 with social anxiety disorder. Venlafaxine ER was significantly more effective than placebo in decreasing social anxiety disorder symptoms with response rates of 56% in the active medication group compared with 37% in the placebo group. Side effects in the venlafaxine participants included anorexia, weight loss, and somnolence. Suicidal ideation was reported in 2% of the youth in the venlafaxine group versus none of those receiving placebo.

Rynn and colleagues (176) compared 12 weeks of venlafaxine ER versus placebo in 323 children and adolescents aged 6–17 with GAD. This report pooled the data from two studies of venlafaxine ER. Maximum venlafaxine dose was 75 mg in youth weighing 25–33 kg, 112.5 mg in participants weighing 34–49 kg and 225 in those weighing more than 50 kg. Venlafaxine was found to be significantly better than placebo in decreasing anxiety symptoms. The response rate to venlafaxine was 69% compared with a placebo response rate of 48%. These studies provide some support for the use of SNRIs (e.g., venlafaxine) in the treatment of children and adolescents with GAD and/or social anxiety disorder.

21.10.2.3. Atomoxetine

Atomoxetine, a selective norepinephrine reuptake inhibitor, was studied in youths aged 8–17 years with ADHD and comorbid anxiety disorder (i.e., SAD, GAD, and/or social anxiety disorder) (177). Participants were randomized to 12 weeks of atomoxetine ($n=87$) versus 12 weeks of placebo ($n=89$). Atomoxetine was initiated at 0.8 mg/kg/day, then increased to a target dose of 1.2 mg/kg/day, and finally increased to 1.8 mg/kg/day, if needed. Sixty-six participants in each condition completed the study. Using last observation carried forward analyses with all randomized participants, the atomoxetine group compared with the placebo group showed significant improvement on rating scales for both ADHD and anxiety symptoms. These findings are promising since comorbid anxiety disorders occur in approximately 25% of children with ADHD (178, 179). Atomoxetine provides an option for treatment of comorbid anxiety disorder and ADHD.

21.10.2.4. Tricyclic Antidepressants

Five small placebo-controlled studies of tricyclic antidepressants (TCAs) for SAD or school refusal show contrasting results (180–184). One study supports the efficacy of a TCA for SAD (183) and another study supports the use of a TCA in combination with individual CBT as more efficacious than placebo combined with individual CBT for anxious-depressed adolescents with severe symptoms (181). The other three studies show no significant differences between a TCA and placebo in decreasing anxiety symptoms and/or facilitating a return to school; however, there are methodological shortcomings in these studies due to low medication dosage (180) or small sample sizes (182, 184). These studies suggest that a TCA may be considered for treating anxiety symptoms in children and adolescents. The presence of a comorbid condition, such as enuresis or ADHD, may be a factor supporting the choice of treatment with a TCA.

TCAs have several drawbacks including the need to monitor electrocardiograms due to the effects that TCAs can have on heart rate and rhythm and to follow blood levels to document that a therapeutic serum level has been achieved. In addition, TCAs may be associated with side effects including dry mouth, sedation, constipation, lightheadedness, weight gain, and urinary retention. Furthermore, overdose with TCAs is dangerous. Due to these drawbacks and the inconsistent findings regarding their efficacy, TCAs are a second-line choice for treating anxiety disorders in children.

Clomipramine, a TCA with serotonergic properties, is strongly supported in the literature as efficacious in the treatment of OCD in children (185–187). Clomipramine was the first drug that was US Food and Drug Administration (FDA) approved for pediatric OCD in 1989 (188). Subsequently, fluoxetine, fluvoxamine, and sertraline were FDA approved for OCD in children and adolescents (188). Several large multicenter, randomized, placebo-controlled trials have demonstrated the efficacy of SSRIs in the treatment of OCD in children and adolescents, including studies of sertraline (189), fluvoxamine (190), fluoxetine (191), and paroxetine (192). A meta-analysis of 12 randomized, controlled studies compared SSRIs (fluoxetine, fluvoxamine, paroxetine, sertraline) and clomipramine in the treatment of OCD in youth ($N=1{,}044$) (193). Multivariate regression analysis of drug effects demonstrated that clomipramine was significantly superior to each of the SSRIs, and the different SSRIs were equally effective in targeting OCD symptoms. However, clomipramine is typically not the first-line choice in treating uncomplicated OCD. Clomipramine is usually reserved for treatment or augmentation in severely symptomatic children or children who have failed SSRIs (193).

21.10.2.5. Benzodiazepines

Research data are lacking regarding efficacy, tolerability and safety (especially long-term). Benzodiazepines may be used on a short-term basis while waiting for the benefits of an SSRI, SNRI, or TCA to be appreciated.

21.10.2.6. Black Box Warning

The Food and Drug Administration (FDA) has issued a black box warning for antidepressant use in children and adolescents. The black box labeling requires that physicians inform families about the small risk of children, adolescents, and young adults developing suicidal ideation or suicidal behavior while receiving an SSRI or another antidepressant (194). In addition, the FDA recommends close monitoring of all youth on antidepressants. Critical times to monitor children closely are initiation of the SSRI trial, change of dosage, and during the taper down and discontinuation period.

The FDA issued the black box warning based on a meta-analysis of 21 placebo-controlled studies of antidepressants in youths, including 14 trials of treatment for major depression and 7 trials of treatment for anxiety disorders. The meta-analysis showed that the risk of serious suicidal events (e.g., suicidal ideation necessitating hospitalization, suicide attempt) was 4% on antidepressants versus 2% on placebo, with an incidence rate ratio of 1.95, which represented a significant difference between drug and placebo with respect to risk of suicidal events (195). There were no completed suicides in the studies included in the meta-analysis.

When the meta-analysis was repeated including only the studies of children with anxiety disorders, the incidence rate ratio for serious suicidal events was 1.31, which indicated no significant difference between antidepressant and placebo with respect to suicidal events in anxiety-disordered children (195). In addition, in the CAMS study, SSRIs were not associated with an increased risk of suicidal behavior in youths with anxiety disorders (170). Thus, it appears that the small risk of suicidal ideation and behavior on antidepressants is less likely in youths with an anxiety disorder compared with youths having major depression (195).

Due to the efficacy of SSRIs (156, 166–170), low incidence of serious suicidal events in youth on antidepressants, and the potential for serious negative outcomes in youth with untreated anxiety, there is strong support for the carefully monitored, appropriate use of SSRIs in the treatment of children and adolescents with anxiety disorders (196, 197). The black box warning should not preclude physicians from prescribing SSRIs when indicated.

21.10.3. Multimodal Treatment Studies

One large study evaluated multimodal treatment for SAD, GAD, and social anxiety disorder (170) and another assessed multimodal treatment for pediatric OCD (156). CBT, sertraline, and their combination were compared in their treatment of SAD, GAD, and social anxiety disorder in the Child-Adolescent Anxiety Multimodal Study (CAMS) (170). Youths aged 7 through 17 years ($N=488$) were randomized to one of the active treatments or pill placebo. The CBT was conducted according to the Coping Cat Program (198). Participants were significantly less likely to withdraw from the CBT condition than the sertraline or placebo groups. Clinical response was evaluated using the Clinical Global Impression (CGI) Improvement scale (199). Combination treatment (80.7% improved) was significantly superior to CBT (59.7%) and sertraline (54.9%) which were not significantly different. All three active treatments were superior to placebo. Based on these results, the authors indicated that CBT for childhood anxiety disorders qualifies as a well-established, evidence-based treatment (200). Combining these results with those from other studies, the authors deem SSRIs to be the class of medication of choice for childhood anxiety disorders. Importantly, in comparison with studies of SSRIs for youths with major depression, SSRIs do not seem to increase suicide risk for youths with anxiety disorders. Finally, the authors stated that while combination treatment may present the most effective treatment for youths with anxiety disorders, both monotherapies were effective, so family preferences should be taken into consideration when providing treatment recommendations. Of note, on average, children demonstrated improvement more quickly when treated with the SSRI in comparison with CBT (170). Consequently, providers may wish to inform parents that CBT may take slightly more time than an SSRI to demonstrate an effect.

In addition to response rates—the percentage demonstrating meaningful improvement in symptoms—remission, or the state of being nearly symptom-free, is an important finding (201). A follow-up study to the CAMS assessed remission based on loss of anxiety diagnoses targeted by treatment. For all treatment groups, remission rates were lower than response rates. The remission rate for combination treatment was superior to CBT alone and sertraline alone which were equal to one another and participants in all three active treatments were more likely to remit than those in the placebo condition. The following variables predicted a youth being less likely to reach remission: older age, minority racial/ethnic status, higher baseline anxiety, diagnosis of social anxiety disorder, and comorbid internalizing disorder (i.e., anxiety, depression).

The Pediatric OCD Treatment Study (POTS) was conducted to compare the efficacy of CBT alone, sertraline alone, and the combination of sertraline and CBT for children and adolescents with OCD (156). One hundred and twelve youths aged 7 through 17 years were randomized to one of the three active treatments or pill placebo. The CBT was conducted in accordance with a treatment manual considered the standard of care for CBT for OCD (202). The primary outcome measure was the CY-BOCS (42). Based on regression analyses of scores from the CY-BOCS, combination treatment was superior to CBT and sertraline which did not differ from one another and both monotherapies were superior to placebo. The percentages in each group that were deemed to have reached remission were as follows: combination (53.6%), CBT (39.3%), sertraline (21.4%), and placebo (3.6%). Effect sizes for the active treatments were as follows: combined (1.4), CBT alone (0.97), and sertraline alone (0.67). Based on these results, the authors recommended that either combination therapy or CBT should be the initial treatment for youths with OCD.

Secondary analyses have been conducted looking at predictors and moderators of outcomes from POTS (203). The following variables were predictors of a poorer response to treatment: higher baseline OCD symptom severity, higher OCD-related functional impairment (per parent report), higher comorbid externalizing symptoms, and higher levels of parental accommodation (i.e., participation in child's OCD rituals and modification of family routines due to child's OCD symptoms). Based on these predictors, youths with greater symptom severity may benefit from longer or more frequent sessions. Youths with externalizing difficulties may also require additional modes of intervention. Family history of OCD was found to moderate response to treatment such that the effect sizes were smaller for all treatments, with the effect size for CBT being 6.5 times smaller for those with a family history of OCD. Garcia et al. (203) noted that when a parent has a history of OCD, it may be difficult for him/her to assist with CBT homework, and consequently it was suggested that youths with OCD with a positive family history might benefit from CBT being conducted in conjunction with pharmacotherapy.

A follow-up study to POTS has been completed (POTS II) (204) to investigate the efficacy of augmenting an SSRI with either CBT or a brief instructional form of CBT conducted by psychiatrists. Once study psychiatrists determined that youths had experienced a partial response to an adequate SSRI trial, they were randomized to one of three conditions: medication management only, medication management plus CBT, or medication management plus instruction in CBT. Youths randomized to the medication-management-only arm were maintained on whichever medication they were taking when they participated in their study entry evaluation. The CBT protocol was the same as the one utilized in POTS. Regarding baseline characteristics, 59.7% of the total sample was diagnosed with at least one comorbid condition (ADHD, anxiety/mood, tic disorder, externalizing disorders). Groups were compared on the percentages with at least a 30% reduction in CY-BOCS score over 12 weeks. Medication plus CBT (68.6%) was significantly superior to the medication plus instructions in CBT (34%) which was equal to the medication-only condition (30%). The authors suggested that these findings reveal the need for greater dissemination into communities of the complete CBT protocols, rather than attempts to abbreviate the treatment.

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22
Schizophrenia in Children and Adolescents

S. Charles Schulz, M.D. and Danielle Goerke, D.O.

Abstract This chapter discusses schizophrenia as it occurs in children and adolescents. Because of the complexity of diagnosis of schizophrenia in children and adolescents, this issue is discussed, followed by a discussion of the epidemiology of the illness in this population. Research into the pathophysiology of schizophrenia in youth is reviewed, including studies of genetics, brain imaging, and neuropsychology. Finally, treatment options, including medication and psychosocial interventions, are discussed.

Keywords Adolescent · Antipsychotic medications · Brain imaging · Neuropsychology · Schizophrenia

22.1. Introduction

Increased attention has been paid to schizophrenia occurring in children and adolescents during the last 20 years, after many years of neglect. Contributing factors to the increased visibility of schizophrenia in young people include publication of the results of brain imaging studies in adolescents suffering from schizophrenia demonstrating that the imaging findings that have become established in adults are present in young people. For many in the field, these changes in the brain were surprising and focused attention on the seriousness of schizophrenia when it occurs in young people. In addition to the emergence of studies examining the structure and function of the brain, there has been a focus on the impact of duration of untreated psychosis (DUP) on overall outcome. With the emergence of recognition that the longer a person is psychotic before their initial treatment, the poorer the person's overall outcome, the focus has expanded to adolescents as well as young adults. Thirdly, first-line atypical antipsychotic medications have been available for the last 30 years and are now approved for the treatment of schizophrenia in both teenagers and adults. Because the traditional antipsychotic medications were seen to cause substantial difficulties with movement disorder, assessment of the new medications for teenagers has increased rapidly in recent years. Therefore, at this time, significantly more attention is focusing on young people than in the past, when schizophrenia in children and adolescents may have been considered to be rare, not part of the adult illness, and difficult to treat with medication (1).

It is the goal of this chapter to address the fundamentals of schizophrenia as it occurs in young people. First, diagnostic issues as they relate to children and adolescents are discussed, followed by an assessment of the prevalence of the illness. Because schizophrenia frequently has its onset during the adolescent years, a discussion of the initial evaluation of a psychotic young person is described. Next, research into the pathophysiology of schizophrenia in youth is reviewed, along with neuropsychological assessments. Second-generation antipsychotic medications offer significant promise for adolescents with schizophrenia, and the status of research in psychopharmacology is reviewed. In closing, the chapter discusses psychosocial interventions for psychotic youth, including family issues of child and adolescent-onset schizophrenia.

S.C. Schulz, M.D. (✉)
Professor, Donald W. Hastings Endowed Chair, Department of Psychiatry,
University of Minnesota School of Medicine, Minneapolis, MN, USA
e-mail: scs@umn.edu

D. Goerke, D.O.
Assistant Professor, Department of Psychiatry, University of Minnesota School of Medicine, Minneapolis, MN, USA
e-mail: dgoerke@umn.edu

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22.2. Diagnosis

For many psychiatric illnesses in adults, diagnosis is a relatively straightforward topic. In schizophrenia occurring in children and adolescents, diagnosis is somewhat more controversial because, for many years, schizophrenia was considered difficult to diagnose, psychosis was seen by some as a phenomenon that could occur under stress during teenage years, and some considered that symptoms seen in adults did not occur in the same fashion in young people.

Starting with the diagnosis of schizophrenia during the adolescent years, it is now well accepted that teenagers can have symptoms similar to those seen in adults. In fact, approximately one-third of people who develop schizophrenia will experience the onset of illness before the age of 18 years (2). When the criteria outlined in the *Diagnostic and Statistical Manual*, 5th edition (DSM-5), are fulfilled, it is appropriate to classify them as having schizophreniform disorder or schizophrenia, depending on the length of the symptoms. Another issue that has been debated is the stability of schizophrenia in youth. Many clinicians were concerned by reports emerging in the 1970s that adolescents on an inpatient service frequently were diagnosed as having schizophrenia at the outset of their symptoms, yet their illness "clarified" itself as bipolar disorder later on (1). This was of significant practical importance to clinicians who did not want to treat patients with neuroleptics unnecessarily. Follow-up studies of first-episode adolescents performed in Suffolk County went on to illustrate that, with training in objective diagnostic tools, the diagnosis of schizophrenia can be reliably made by psychiatrists. Furthermore, follow-up studies indicated that the diagnosis of schizophrenia was accurate in 95% of the adolescents 6 months after being diagnosed and that conversion to bipolar disorder in these rigorously identified youth was uncommon (3).

The discussion of the characteristics of adolescents with schizophrenia portrays the issue of diagnosis in an overly simplistic fashion. Clinicians are faced with how to diagnose a youth with psychosis, not with how to validate the diagnosis of schizophrenia. Clearly, not every psychotic youth suffers from schizophrenia. Research at the National Institute of Mental Health indicated many referrals to the Schizophrenia Research Project ended up with a final diagnosis that was not schizophrenia. For example, some youths were given the diagnosis of multidimensional impairment—an illness with some psychotic features but not those that would qualify for a schizophrenic diagnosis (4).

To add to the complexity of diagnosis of schizophrenia in youth, has come recent attention on the prodrome of schizophrenia. Prodromal symptoms are nonspecific complaints that can precede the illness from some weeks up to years before specific symptoms of schizophrenia occur (5, 6). Investigators around the world examining first-episode psychosis have begun investigating the characteristics of the prodrome, and many of these investigators have focused their attention on adolescents. White and colleagues (7) note that nonspecific symptoms such as difficulties with sustained attention, social withdrawal, cognitive decline (decreased performance in school), and brief psychotic-like symptoms can precede the onset of schizophrenia. The approach to the assessment of such states in adolescents and young adults was conceptualized in the Comprehensive Assessment of At-Risk Mental States (CAARMS) by Yung et al. in Australia (8). The intention of the CAARMS was to identify those at the greatest risk of conversion to a first episode of psychosis from a prodromal state in order to reduce the duration of untreated psychosis. The Structured Instrument for Prodromal Syndromes (SIPS) was developed by the Prevention through Risk Identification, Management, and Education (PRIME) prodromal research team at Yale University and is more widely used in the United States for this same purpose (9).

Therefore, recent research indicates that the diagnosis of schizophrenia can be applied to children and to adolescents using criteria from DSM-5 (10). The criteria are the same as those in adults, and once the diagnosis has been made, they seem to be diagnostically stable over time. Nonetheless, not all psychoses are schizophrenia and a careful history from patients and their families or other informants is important in making a final diagnosis. White et al. (7) go on to note the importance of physical and neurological examination—often paired with neuropsychological testing and brain imaging. The use of structured interviews in research programs can sometimes assist in difficult cases to make sure all areas are assessed.

22.3. Epidemiology

It is well known from worldwide epidemiologic studies that schizophrenia is present in approximately 1% of the population (11). The relatively common prevalence is caused, in part, by the long course of the illness. Clearly, teenagers do not have schizophrenia at a prevalence of 1%; however, a number of epidemiologic studies point to some interesting characteristics of schizophrenia in young people. The first epidemiologic finding is that schizophrenia is rare in children before the onset of puberty. Studies indicate a prevalence of schizophrenia of 1 in 10,000 in children (12). Interestingly, boys and girls have similar rates of schizophrenia before the onset of puberty.

Beginning with early adolescence, the rates of onset of schizophrenia begin to rapidly increase. It is well known that this increase is faster in boys than in girls. For example, Loranger has reported that as many as 40% of young men first hospitalized for psychosis reported their symptoms began before age 19 years (2). This figure drops to 26% for young women. Another

first-episode study that is informative for the onset of schizophrenia is that of Hafner in Germany, a country with universal health coverage. Therefore, the epidemiologic sampling may be more accurate than seen in some US studies. Hafner's work clearly illustrates the rapid rise in the onset of schizophrenia in adolescence, with an approximate 4-year difference in rates between young men and young women (13).

As rates of an illness and its age of onset are part of epidemiology, so is the course of the illness. One again turns to countries with universal healthcare coverage and national medical health records for studies on the outcome of teenagers suffering from schizophrenia. German studies, such as those by Ropcke and Eggers (14), illustrate that early-onset schizophrenia (younger than age 18 years) is associated with a relatively poor outcome. In their follow-up study, "severe" or "very severe" outcome was noted for 51% of patients who had early-onset schizophrenia when assessed 15 years later.

In summary, the epidemiology of schizophrenia in youth is of interest to the field, because it is a time of rapid increase in the onset of the illness and a time in which male patients illustrate a highly significant earlier onset of the disease. Furthermore, the curious finding of poor outcome in the earlier onset cases has been noted and explored by investigators and raises concern for clinicians. It remains to be determined whether the reported poor outcome in children and teenagers is caused by earlier forms of schizophrenia being more severe or whether delays in initiation of treatment lead to poorer outcome.

22.4. Pathophysiology

22.4.1. Genetics

It is well known that genetic epidemiology studies have consistently demonstrated a family aggregation for schizophrenia. Supporting a genetic hypothesis of schizophrenia, the family aggregation increases in prevalence with the degree of relatedness. For example, siblings of a person who has schizophrenia have rates of schizophrenia of 8%, whereas identical twins have concordance rates of nearly 50% (15). In addition, the family aggregation is not changed by being raised by an adoptive family (16, 17). With the emerging technology of molecular biology, there have been a large number of genes that are statistically associated with schizophrenia. Though no one gene has been identified as specific to those afflicted with schizophrenia, many of these genes are known to be associated with synaptic development and neuronal plasticity (18). Supporting the neurodevelopmental theory of schizophrenia are whole-genome studies showing genetic overlap between patients with autism, schizophrenia, and bipolar disorder. Findings suggest schizophrenia, autism, and other neurodevelopmental disorders may share underlying pathogenic mechanisms (19, 20).

22.4.2. Brain Imaging

Because symptoms of schizophrenia or its prodrome can frequently begin during adolescence, researchers have theorized that developmental events during adolescence may be related to the onset of the disease. A theory long at the forefront of this line of investigation was introduced by Feinberg (21) and states that the onset of symptoms of schizophrenia is the result of abnormal pruning of neural connections—a normal stage of neural development. As theories of neurodevelopment emerged to explain certain characteristics of schizophrenia, Keshavan et al. (22) described two events that could underlie schizophrenia—a neurodevelopmental alteration and a later pruning abnormality.

Interestingly, white matter, the connecting matter of the brain cells, is also continuing to develop in adolescence and early adulthood. Some have theorized that changes in white matter development may lead to a connectivity disturbance that could underlie symptoms such as unconnected thoughts or perceptions. In adults, Lim and colleagues (23) have shown decreased white matter integrity in imaged brains of adults with schizophrenia. White and colleagues (24) have shown white matter abnormalities in the hippocampal region of the brain in adolescents with schizophrenia. Figure 22.1 illustrates this finding.

The development of noninvasive brain imaging during the 1970s opened a new vista in schizophrenia research allowing investigators to assess the brain in large groups of subjects for the first time. Research quickly moved from the demonstration that schizophrenic patients had structural differences compared with control subjects in computed tomography (CT) (25, 26) and magnetic resonance imaging (MRI) studies (27) to showing functional changes using positron emission tomography (PET) scanning and functional MRI (28). Related to some of the theories that may have special relevance to adolescent-onset schizophrenia, MRI scanners using spectroscopic techniques can measure substances related to neuronal mass—*N*-acetyl aspartate (29) or neurotransmitters such as glutamate (30). These imaging tools have been increasingly applied to the study of schizophrenia as well as other serious psychiatric illnesses, revealing more and more about the brain. What has been found about child and adolescent schizophrenia is described next.

Initial studies of adolescents with schizophrenia used CT scans and reported that those younger than 18 years old had ventricle size larger than control subjects (31, 32). The authors noted the similarity to findings in adults and consistency with the

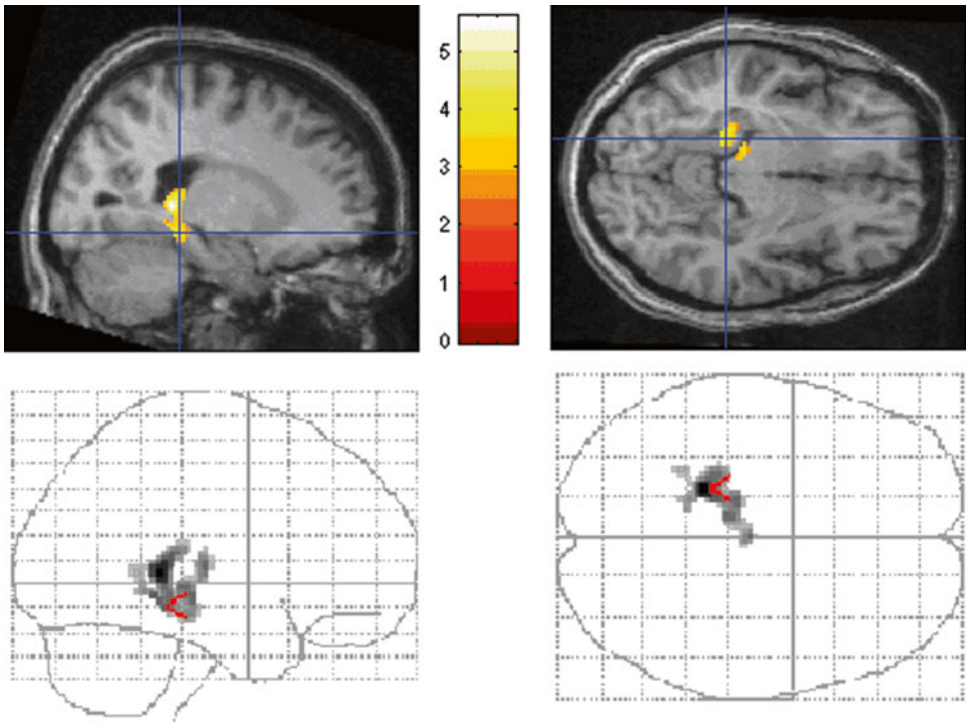

FIGURE 22.1. Reduction of fractional anisotropy (FA) in the posterior hippocampus in children and adolescents with schizophrenia compared to controls. The figures on the *top* demonstrate areas of decreased FA on the sagittal (*left*) and axial (*right*) images. The *lower images* correspond to the same orientation as those above and are presented in a "glass brain" format. These *lower images* demonstrate the focal location of hippocampal FA differences (Figure courtesy of the Youth Psychosis Research Group at the University of Minnesota).

neurodevelopmental model of schizophrenia. Later, MRI structural scans noted differences from control subjects in the ventricular as well as cortical areas of the brain (33, 34).

The structural studies led to the conclusion that adolescent schizophrenia (or childhood-onset schizophrenia studied during adolescence) was not a special form of the illness and that it was essentially on a continuum with the adult form of the disease (1).

However, following from these reports, longitudinal studies from the NIMH research group found that there may be brain changes over time—a result that was inconsistent with MRI studies up to that point. The enlargement of ventricles over 2 years in adolescents challenged tenets of the neurodevelopmental hypotheses and antedated results of first-episode studies in young adults (35, 36). These dynamic changes in brain at the onset of the illness will lead to further interesting research.

Another form of structural imaging is diffusion tensor imaging (DTI), which measures the integrity of white matter—the connecting wiring of the brain. Studies of white matter in teenagers have demonstrated differences from similarly aged control groups—a finding located in the posterior temporal lobe (hippocampal area), which may represent a critical connection in thinking and perception (24).

Brain functioning has become amenable to imaging research through the development of both PET scanning assessment of glucose metabolism in neurons to functional MRI that assesses regional blood flow—usually under specific conditions such as cognitive testing. Investigators of adolescents have shown that schizophrenic subjects have functional differences from control subjects in PET scanning (37). This paper indicated a resting difference in metabolism in this sample of young people.

In summary, brain imaging studies demonstrated that brain structure—both gross and microstructure (DTI)—are similar in nature, if not in degree, to adult forms of schizophrenia. The significance of this line of research is unfolding as investigators explore possible developmental deviations to find whether they relate to symptom development. Others point to the imaging studies to underscore the seriousness of the illness in teenagers and the need for the recognition of the illness and the timely implementation of appropriate treatment.

22.4.3. Neuropsychology

As with brain imaging, the neuropsychological assessments performed in adults with schizophrenia have been applied to adolescents with schizophrenia. One purpose of such studies was to pursue functional brain properties that might compliment

imaging studies; but, in addition, neuropsychological testing was seen to potentially assist in treatment planning by quantifying cognitive strengths or weaknesses.

The first neuropsychological testing research report noted that adolescents with schizophrenia had statistically significant deficits compared with a control group (38). The greatest differences were in attention and memory domains of the test battery, but not in the area of executive function, as has been seen in adults. White and colleagues (7) noted, in a second study, that perhaps one of the reasons adolescents with schizophrenia are not different from control subjects is that executive function in teenagers is still developing and not yet up to adult levels.

The course of neuropsychological functioning has been examined by Wozniak and colleagues (39), and they have found a remarkable stability during the 1-year follow-up period. This study, which is consistent with a first-episode study conducted by Hoff and colleagues (40), illustrated a paradox in that adolescent and first-episode studies of structured brain imaging show a progression of deficits, whereas wide-ranging cognitive assessments do not.

More recently the neuropsychological profiles of patients with familial high risk (FHR) to develop a primary psychotic disorder or those considered clinically high risk (CHR) as evidenced by attenuated psychotic symptoms (APS) or having experienced brief limited intermittent psychotic symptoms (BLIPS) have been investigated. The intention being twofold; to further classify at which point in the progression of psychotic illness cognitive impairment develops as a target for intervention and to identify potential neuropsychological impairments that could be used as early markers to predict which at-risk youth are likely to progress to a primary psychotic disorder. These studies have consistently demonstrated that those with FHR show neuropsychological deficits less severe than those that meet criteria for being CHR. However, once a patient meets criteria for CHR, neuropsychological deficits, albeit present, are still not as severe as their first-episode counterparts (41–46).

22.4.4. Summary

The use of imaging and neuropsychological testing has made a major impact on psychiatric research as a whole, and because it is noninvasive, it has great potential in young people to extend the studies described above. To date, both of these research tools have demonstrated many similarities between adolescents and adults suffering from schizophrenia. Many clinical investigators have offered the opinion that the findings underscore the seriousness of psychosis in teenagers and the need for assertive treatment that is described in the next section.

22.5. Treatment of Schizophrenia in Children and Adolescents

22.5.1. The Comprehensive Approach

In adult patients suffering from schizophrenia, medication treatment provides a platform for the reduction of the positive symptoms of the illness. Studies supporting the efficacy of antipsychotic medications—first- and second-generation medications—are well supported by clinical trials (47–49). Furthermore, in the last 25 years, empirically supported specific psychosocial interventions have been developed that are significantly better than treatments as usual in both reducing symptoms and in decreasing relapse (50).

Only recently have a limited number of trials supporting the efficacy of antipsychotic medications in children and adolescents with schizophrenia been completed. Positive treatment outcomes in these studies have led to the FDA approval of several antipsychotic medications in this patient population.

Interestingly, as discussed in the earlier sections of this chapter, young people developing schizophrenia may face a more difficult course, yet there is a paucity of psychosocial treatments, in which controlled trials of family psychoeducation, social skills treatment, and cognitive rehabilitation treatment are underdeveloped for this age group. The lack of data for the treatment of children and adolescents with schizophrenia comes at a time when a number of studies are emerging regarding the impact of duration of untreated psychosis (DUP) on social and functional outcomes (51).

Therefore, the purpose of this section of the chapter is to focus on the status of medication interventions for children and adolescents suffering from schizophrenia—special attention is focused on adolescents, because few studies have been performed for patients younger than age 13 years. Second, psychosocial treatment approaches are discussed, with a focus on family psychoeducation and support as well as cognitive rehabilitation strategies.

22.5.2. Medications

As noted above, the platform for treatment in adults suffering from schizophrenia during the last 50 years has been the use of antipsychotic medications. Such studies have demonstrated the efficacy of antipsychotic medications, in particular the positive symptoms associated with schizophrenia and as maintenance to prevent subsequent episodes (49).

As noted above, the traditional or first-generation antipsychotic medications did not receive extensive attention in young people. Interestingly, there is only one double-blind, placebo-controlled trial of traditional antipsychotic medications—that by Pool and colleagues in 1976. This study investigated loxapine and haloperidol compared with placebo and did find a statistically significant advantage for these two medications, one of which was considered to be a sedating compound and the other a high-potency drug. The other controlled study of traditional antipsychotic medications compared two somewhat dissimilar compounds (thiothixene and thioridazine) and found an equivalent outcome for both in which patients improved throughout the study. Unfortunately, in the second study, the authors concluded that the tolerability of the compounds was so poor in teenagers, secondary to involuntary movement disorders, that an adequate dose was frequently difficult to reach (52).

In preteens, there is one controlled study (53) investigating haloperidol for children. This trial also shows an advantage for this traditional antipsychotic medication at a dose of 0.5–3.5 mg/day yet is of such a small subject number that it is difficult to translate into clinical treatment planning. However, for prepubertal patients, antipsychotic medications are widely used.

Therefore, through the 1980s and early 1990s, the field of child and adolescent psychiatry addressed the treatment of schizophrenic patients with little to guide them regarding the choice of medication, the dosing strategy, or the awareness of differential side effects in children and adolescents.

The research field in schizophrenia focused on the difficulties accompanying traditional antipsychotic medication treatment, which frequently led to movement disorders. The advent of the atypical antipsychotics—second-generation antipsychotics—led many to theorize that, without movement disorder side effects, young people could be more adequately treated.

To investigate this line of reasoning, several case series of medications were initiated. Risperidone was the first approved second-generation antipsychotic medication, and early studies reported usefulness in adolescents suffering from schizophrenia at doses now considered to be in the high range even for adults. The trials reported a significant reduction in positive and negative symptoms (54–57). Early case series with patients younger than age 18 years reported good tolerability for risperidone treatment, especially in the area of movement disorders.

After these studies were reported, hormonally related side effects began to be published in the literature (58). Symptoms such as galactorrhea, gynecomastia, breast tenderness, and erectile dysfunction—symptoms that were probably related to the impact of risperidone on prolactin—were reported. These symptoms are troublesome for youth, and when risperidone is used in an adolescent population, candid discussion with patients and their families regarding the potential for these side effects should be provided.

Olanzapine was the second of the atypical antipsychotic medications to be approved, and a case series by Findling and colleagues (59) demonstrated the ability of the compound to reduce symptoms of schizophrenia in an adolescent population. Interestingly, doses similar to those seen in adults were arrived at through a flexible dosing strategy used in the trial. The average dose for the adolescent subjects was 12.4 mg. Of concern was the finding that the 15 adolescent patients gained an average of 6.5 kg during the first 8 weeks of the study. This brought to the field's attention the possibility that there may be a differential in the side effect profile in teenagers compared with adults.

The first double-blind, placebo-controlled trial of an atypical antipsychotic medication in teenagers was reported by Kryzhanovskaya et al. (60). In this study of 107 teenagers, there was a statistically significant advantage for olanzapine at a dose of 11.1 mg/day. Interestingly, this is the first placebo-controlled trial for the treatment of schizophrenia in teenagers since the Pool study of the mid-1970s. However, further analysis by Kryzhanovskaya et al. (60) in comparison to data on file at Eli Lilly demonstrated that the subjects in the study may be at higher risk for development of the metabolic syndrome compared with adults. Given this significant risk for metabolic side effects, despite pronounced antipsychotic efficacy, olanzapine is not a first-line agent for the treatment of child and adolescent schizophrenia. However, should alternative atypical antipsychotics prove ineffective, olanzapine should be considered.

The atypical antipsychotic medication, quetiapine, has been tested by two different groups to examine psychotic youth. Studies by McConville et al. (61) showed substantial decreases in psychotic symptoms during a 3-week period. Assessments showed a significant reduction in symptoms in the "indeterminate psychosis" group, and doses up to 800 mg/day were well tolerated. In the longer term, McConville and colleagues (62) reported that, in an open-label extension of 88 weeks in ten subjects, there was continued symptom reduction and no movement disorder side effects. Some weight gain was reported but was not statistically significant. Studies by Shaw and colleagues (63) also illustrated significant reductions in symptoms of psychosis in teenage patients and reported that quetiapine was well tolerated in the patient group. In this study, positive effects were seen in doses of 467 mg/day.

In a report by Jensen and colleagues (64), quetiapine, olanzapine, and risperidone were compared in psychotic teenagers. The purpose of the trial was to evaluate efficacy as well as safety in the treatment outcome of teenaged patients with psychotic illnesses broadly defined. The results illustrated that, in general, the three compounds were useful in teenagers with schizophrenia and that risperidone led to statistically significant improvement compared with quetiapine on one of the rating scales. On the other hand, quetiapine was very well tolerated in the teenaged patients. All three agents resulted in significant weight gain.

The other comparison trial in adolescents examined olanzapine and risperidone versus the typical antipsychotic agent haloperidol. All three medications led to symptom reduction. The authors noted weight gain and extrapyramidal side effects (EPS) for subjects undergoing atypical antipsychotic treatment that seemed greater than in adults (65).

An area infrequently discussed in child and adolescent schizophrenia is the management of patients who are not responsive to initial, first-line atypical antipsychotic medication. The rates of nonresponse in adolescent patients have not been well addressed, but data from first-episode studies indicate that nearly a quarter of patients are not responders in the first year (35). As noted earlier, childhood- onset and adolescent-onset schizophrenia patients may have a poor outcome as a group, and therefore, attention to early nonresponse may improve the course of illness.

The only medication with empiric support for nonresponders is clozapine, a medication demonstrated to be significantly superior to other medications for persistently ill patients (66). Evidence for the use of clozapine comes from the NIMH, where Kumra et al. (67) tested clozapine versus haloperidol in refractory childhood-onset schizophrenic patients. The group's work showed the advantage of clozapine in this young group. In addition, they reported the side effects seen in teenagers—seizures and low white blood cell count—that must be watched for in this group (67).

European studies have reinforced these findings, because Remschmidt and colleagues have reported on 36 schizophrenic patients treated with clozapine (68). The group later summarized their clinical recommendations for using clozapine in adolescents with schizophrenia, noting clozapine's efficacy in this patient group and the lower rates of movement disorders. They also note the importance of being aware of side effects—agranulocytosis, seizures, fever, weight gain, and tachycardia (69).

Aripiprazole is a second-generation antipsychotic medication with partial dopamine agonist properties—a different action on the dopamine receptors than the other antipsychotic medications. Aripiprazole has also been tested in adolescents in a double-blind placebo-controlled trial showing a statistically significant advantage in the treatment of psychotic symptoms. While higher doses (30 mg) daily did result in earlier improvement, the 10 mg dose also resulted in clinical improvement. Though fewer metabolic side effects have been reported, complaints of akathisia were statistically significant (70).

Ziprasidone was frequently used for adolescents with schizophrenia when first released because of a lower propensity for causing weight gain than other atypical antipsychotic medications. Ziprasidone given to adolescents at doses ranging from 80 to 160 mg did not result in improvement of brief psychiatric rating scale-anchored (BPRS-A) scale over placebo (71).

When designing the treatment regimen for young people with schizophrenia, clinicians should be aware of the potential for exaggerated side effects as compared to adults. Lowest effective doses of medications with the fewest potential side effects should first be tried. However, it is clear that the benefits of using atypical antipsychotics in this population as evidenced by reduction of positive psychotic symptoms which in turn improves quality of life, function and reduces the risk of suicide, outweighs the risk of potential side effects. Recent years have brought increased attention to young people with schizophrenia—especially those in childhood and adolescence. It is hoped that neuroscience research can advance the field's knowledge regarding schizophrenia as well as providing tangible results regarding the illness and its treatment of youth.

22.5.3. Psychosocial Treatment

Treatment of children and adolescents with schizophrenia requires substantial psychosocial treatment for success. Approaches demonstrated to reduce symptoms and forestall relapse in adults are used to treat adolescent patients with schizophrenia.

Sikich (72) has carefully reviewed therapy approaches for psychotic youth and noted the added benefit of cognitive behavioral therapy to medication. Further, she noted the importance of assessing the stage of illness to tailor treatment—for example, working with a person in the prodrome versus established schizophrenia. She also describes how newer techniques including a cognitive remediation approach may be helpful.

Many children and adolescents will require increased academic support following the diagnosis and while engaging in treatment. Contact with the school to engage guidance counselors and initiate individualized education plans can often be beneficial. The cognitive deficits associated with psychosis mimic those experienced with attention deficit disorders, and often-similar classroom accommodations (sitting in the front of the room, increased test-taking time in quiet environment) can be helpful. Early in the treatment course, the use of in-home-modified curriculum may be necessary.

Some of our work with families of adolescents with schizophrenia discussed the importance of engagement with families (73). Interestingly, their feedback indicated that barraging them with information too quickly was distressing. They communicated that a careful titration of the balance of the seriousness of the illness with hopefulness was needed.

22.6. Conclusions

Just a few decades ago, the field of psychiatry generally conceived of psychosis in adolescents as a reaction to stress, perhaps on top of a difficult developmental step. Biological factors were not thought to play a significant role in the illness, and pharmacotherapy was frequently avoided.

As has been presented in this book, *The Medical Basis of Psychiatry*, there have been significant changes that have shown a continuum between adolescent and adult forms of schizophrenia when brain imaging and neuropsychological assessments have been applied. In fact, some would say that the use of these tools during the active neurodevelopmental step of adolescence might offer opportunities not present at other stages of the disease.

Treatment has also begun to evolve despite very significant challenges facing those prescribing medications for young schizophrenic patients. Just as new medications seemed to offer hope that atypical antipsychotic medications would be efficacious for treatment of psychosis without movement side effects, some of the most recent studies are cautionary regarding metabolic issues. Further, psychosocial treatment research, which has shown a number of specific interventions in adult schizophrenia, requires much more development in youth.

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Part III
Symptom Clusters

23
Mood Disturbances

Hagop S. Akiskal, M.D.

Abstract Mood or affective disturbances are common expressions of mental and systemic diseases. We distinguish normative emotions such as grief, sadness, joy, anger and fear from their elaboration into depressive, manic, and mixed syndromes in unipolar and bipolar disorders. We then differentiate normative anxiety disorders from depressive illness along clinical and biologic parameters. The differential diagnosis of mood disorders from dementia and schizophrenia is taken up next in terms of natural history and biology. In-depth descriptions of the signs and symptoms of mood disorders are covered under emotional, cognitive, psychomotor, and vegetative subheadings. We finally give coverage to the chronic and subthreshold mood disorders, including dysthymia and cyclothymia. Knowledge of the psychopathology of mood disorders and their variants is of immense public health significance in light of their consequences in educational, conjugal, vocational, and physical health areas and, more seriously, in their potential for suicidality.

Keywords Affect · Mood · Mood disorders · Mania · Depression · Mixed state · Bipolar disorder · Suicidality

23.1. Affects, Moods, and Their Disorders

Disturbances in the sphere of affect and mood, especially depressive manifestations, are among the most common signs and symptoms prompting medical consultation, both in psychiatry and in general medical practice. This is not surprising given the fact that, from an evolutionary perspective, affective arousal serves essential communication functions. Affect is something that moves us to appraise, for instance, whether another person is content, dissatisfied, or in danger. *Affect* refers to that aspect of emotion that is expressed through facial expression, vocal inflection, words, gestures, posture, and so on, whereas *mood* denotes more enduring emotional expressions. Joy, sadness, fear, and anger are basic affects, and their expression tells us how an individual feels at any given moment; mood, on the other hand, relates to how one has been feeling over a period of time.

An individual's affective "tone" is thus the barometer of his or her inward emotional well-being. Each individual has a characteristic pattern of basal affective oscillations that defines his or her *temperament*. For instance, some people are minimally touched by adversity or reward and tend to remain placid. In contrast, others are easily moved to tears by sad or happy circumstances, and still others are more prone to fear, worry, or anger. Normally, oscillations in affective tone are relatively minor, tend to resonate with day-to-day events, and do not interfere with functioning.

We speak of affective disturbances when the amplitude and duration of affective change are beyond adaptive demands and lead to impaired function. Such impairment entails disturbances that go beyond subjective mood change and involves pathologic alterations in activity and thought as well. Mood disturbances leading to clinically diagnosable disorders arise in two patterns. The first pattern manifests in episodes which are sustained conglomerations of affective signs and symptoms typically lasting for weeks to months at a time and which tend to recur after variable intervals (typically measured in years). Episodes

H.S. Akiskal, M.D. (✉)
Professor and Director of International Mood Center, Department of Psychiatry, and Division of International Health and Cross-Cultural Medicine, University of California at San Diego, La Jolla, CA, USA
e-mail: hakiskal@ucsd.edu

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TABLE 23.1. The bipolar spectrum.

- Bipolar I (BP-I): depressions alternating with mania or vice versa
- Bipolar II (BP-II): depressions interspersed with hypomanic episodes
- Bipolar III: hypomanic switches on antidepressant treatment or other somatotherapy
- Bipolar IV: depression arising from hyperthymic temperament

can be either depressive in nature (where depressive and associated signs and symptoms dominate the clinical picture), manic (where euphoric and associated signs and symptoms dominate the clinical picture), or mixed (where depressive and manic manifestations coexist simultaneously). In DSM-IV (1), patients with single or recurrent depressive episodes are said to have major depressive disorder, sometimes referred to as *unipolar* and which can occur at any age. Almost all patients with manic and mixed episodes have depressive episodes as well, and for this reason, the illness is known as *bipolar disorder*; its age at onset peaks in younger age groups (teens to the 40s). Bipolar disorder was formerly known as "manic-depressive" illness (2). Although both major depressive and bipolar forms of mood disorders can be precipitated by social or biologic stressors—and this is particularly true for episodes in the early course of these disorders—what characterizes them is that episodes persist autonomously even after these stressors are no longer operative. In brief, recurrent major depressive and bipolar disorders are characterized by pathologically sustained moods and related signs and symptoms that cannot be justified by external circumstances.

The second pattern of affective disturbances consists of fluctuating periods of mood which do not cluster into discrete episodes but instead occur in a low-grade intermittent pattern, typically beginning in late childhood or adolescence and continuing throughout much of adulthood (3). *Dysthymia* is characterized by low-grade depressive manifestations, *hyperthymia* with milder periods of frequent highs known as hypomania, and *cyclothymia* by a variability of moods which alternates between "up" and "down" periods. These three conditions are also known as "subaffective disorders" in the sense that they represent clinically attenuated expressions or *formes frustes* of affective disorders. They can exist throughout life as temperamental extremes without significant pathology but when accentuated can produce at least some impairment in functioning in view of their tendency to be intermittently chronic. In clinical practice, dysthymia and cyclothymia often represent the precursors of major depressive or bipolar disorder or constitute the inter-episodic manifestations to which patients return after recovering from depressive, manic, or mixed episodes.

The unipolar-bipolar distinction described above represents a general framework for mood disorders. Between the extremes of strict unipolar depression (no clear-cut high periods) and bipolar I disorder (depression alternating with full-blown mania or mixed states), there are conditions termed as unipolar II (in which patients develop hypomanic or mild excitements upon antidepressant treatment and for this reason should be more appropriately characterized as "bipolar III") and bipolar II (in which patients have spontaneous hypomania, typically at the tail end of episodes) (4). In some bipolar II patients, the high periods are so frequent that the patients are best described as "cyclothymic depressions." Finally, to complicate matters, there are some unipolar patients who should actually be considered "pseudo-unipolar" because they descend into major depressive episodes from the higher than normal plane of a hyperthymic temperament (5); another term for these patients is "bipolar IV." Much more research needs to be conducted on these intermediate affective conditions for better nosologic assignment. Table 23.1 summarizes the above concepts; of the bipolar subtypes, only bipolar I and bipolar II are officially recognized in the American Psychiatric Association's official nosology (DSM-IV-TR, 2000) (1); in the latter, the term "unipolar" is avoided, because with increasing number of episodes, many major depressive patients switch to bipolar I or II (6, 7). For all the foregoing reasons, the unipolar-bipolar dichotomy is being increasingly challenged in favor of a "bipolar spectrum" (8), sometimes also referred to as a "mood spectrum" (9).

In its pathologic expression, angry affect is not elaborated into a distinct psychopathologic disorder and is generic to a wide variety of psychiatric disorders. Fear, on the other hand, in its pathologic expression known as anxiety, is seen not only secondary to many psychiatric conditions but also elaborated into a spectrum of anxiety disorders. Because DSM-IV-TR limits the rubric of "mood disorder" to conditions characterized by pathologic depression and elation, the discussion of anxiety and anger in this chapter is only to the extent that they represent manifestations of mood disorders.

The primary aim of this chapter, then, is to describe the signs and symptoms of disturbed affect and mood in such detail as to permit their differentiation from normal affective states and the manifestations of other psychiatric disorders.

Whatever their primary specialty, all physicians must be competent in the proper diagnosis and treatment of depressive conditions not only because of their high prevalence but also in view of emerging data on the disabling nature of unrecognized protracted depressions. Indeed, a report published in JAMA (10) has demonstrated that the functional disability induced by such depressions exceeds that of most medical conditions and equals that of cardiac disease. Social consequences appear equally disabling (11). Recent data have extended these findings to bipolar disorder, including bipolar depression (12, 13). Such harmful dysfunction has also been documented in subthreshold bipolar conditions in the community (14).

TABLE 23.2. Medical conditions and pharmacologic agents commonly associated with onset of depression.

Medical conditions
Hypothyroidism
Cushing's disease
Diabetes mellitus
Systemic lupus erythematosus
Myocardial infarction
Avitaminosis
Anemia
Cancer (especially abdominal)
Tuberculosis
Influenza; viral pneumonia
Infectious mononucleosis
General paresis (tertiary syphilis)
Acquired immunodeficiency syndrome (AIDS)
Cerebral tumor
Head trauma
Complex partial seizures (temporal lobe epilepsy)
Stroke
Parkinson's disease
Multiple sclerosis
Alzheimer's disease
Sleep apnea
Pharmacologic agents
Reserpine, alphamethyldopa, other antihypertensives
Anticancer chemotherapy
Corticosteroids, oral contraceptives
Interferon
Cimetidine, indomethacin
Classical antipsychotics
Anticholinesterase insecticides
Alcohol, barbiturates
Stimulant withdrawal

23.2. The Depressive Syndrome

As in other medical conditions, signs and symptoms of depression tend to cluster together in the form of a syndrome, also known as "clinical depression." Depression as a medical syndrome has been known since Hippocratic times, for nearly 2,500 years. Excellent contemporary reviews are provided by Lewis (15) and Jackson (16). Multiple etiologic factors—some genetic, others environmental—can give rise to the final common pathway of depression (17). One group of causative factors that should always be considered in the etiology of depression, especially in patients over the age of 40, is systemic disease or drugs used in their treatment (see Table 23.2). It is not always clear, however, that such diseases are sufficient causes of depression. Typically, not more than 15% of those with one of the conditions listed in the table will suffer from clinical depression. Further, eliminating the offending physical condition, if at all possible, does not necessarily cure the depressive state.

Indeed, those who succumb to depression secondary to somatic conditions often seem to have past personal or familial history for depression. Thus, some form of underlying predisposition, often of genetic nature, seems to be required, especially for recurrent mood disorders. However, the prognosis of the depressive syndrome may vary, depending on whether or not it is superimposed on a medical or a nonaffective psychiatric disorder, such as panic disorder, sociopathy, or schizophrenia (18). These secondary depressions tend to have somewhat atypical clinical features owing to the underlying disorder and often linger for many months (and sometimes years) beyond the usual duration of the depressive syndrome. It is in the syndrome occurring as a primary mood disorder that one observes the most typical manifestations of depressive illness, and whereas the course of secondary depressions is generally dictated by the underlying disorder, many primary depressions tend to recur on the basis of an inherent biologic rhythmicity.

The depressive syndrome is conveniently discussed by considering disturbances in four areas that characterize it: mood, vegetative, psychomotor, and cognitive.

23.2.1. Mood Change

The mood disturbance is usually considered the *sine qua non* of the syndrome and may manifest either in painful arousal or loss of the capacity for pleasurable experiences (anhedonia).

The painful arousal can take the form of extreme sadness, irritability, or anxiety and, in the extreme, is indescribably agonizing. The irritability and anxiety are often qualitatively different from their "neurotic" counterparts and take the form of severe inner turmoil and groundless apprehensions. In the full-blown form of the malady, the sustained nature of the painful mood does not permit distraction even for a moment. The psychic pain of depression is so agonizing that patients often describe it as being beyond ordinary physical pain. William James (19) referred to his depression as "psychical neuralgia." Patients may resort to suicide in an attempt to find deliverance from such tormenting psychic pain. A more recent literary portrayal of the depressive's anguish is William Styron's memoir of his severe bout with the illness (20)—a condition in which "darkness" becomes visible. Other patients, suffering from a milder form of the malady and typically seen in primary-care settings, deny experiencing such mental pain and instead complain of monosymptomatic physical agony in the form of, for example, headache, epigastric pain, and precordial distress; in the absence of any evidence of organically diagnosable pathology, multiple pain is often present, especially in juvenile patients (21). Such conditions have been described as *depressio sine depressione* or masked depression (22). In these situations, the physician can corroborate the presence of mood change by the depressed affect in the facial expression, the voice, and the patient's overall appearance; past or future more typical depression or family history for depression can serve as external validators.

Paradoxically, this heightened perception of pain so characteristic of clinical depression is often accompanied by an inability to experience normal sadness and grief, as well as joy and pleasure. Thus, *anhedonia*, the loss of the ability to experience pleasure, is a special instance of a more generalized inability to experience normal emotions. Patients exhibiting this disturbance often lose the capacity to cry—an ability that may return as the depression is lifting.

During the clinical interview, it is not enough to inquire whether the patient has lost the sense of pleasure; the clinician must document that the patient has given up previously enjoyed pastimes. In the extreme, patients may complain that they have lost all feelings for their children, who once were a source of great joy. The impact of the loss of emotional experience can be so pervasive that patients may give up values and beliefs that had previously given meaning to their lives. This is well described by Tolstoy in his autobiographical confessions (23), in which he describes how his bouts of depression later in life led to "spiritual crises." The depressive's inability to experience normal emotions is different from the blunting seen in schizophrenia in that the loss of emotions is itself experienced as painful; that is, the depressive suffers immensely from his or her inability to experience emotions.

23.2.2. Vegetative Disturbances

The ancients believed that depression was a somatic illness and ascribed it to "black bile," hence the term "melancholia," from the Greek word for this substance. Indeed, the mood change in depressive illness is accompanied by several physiologic disturbances that implicate limbic-diencephalic dysfunction (17). These include changes in libido and menstruation, appetite and sleep, as well as other circadian rhythms. DSM-IV-TR now uses the term "melancholia" for a special cluster of depressive symptomatology that includes marked vegetative and psychomotor disturbances, anhedonia, and self-reproach; these manifestations persist autonomously, showing no reactivity to psychosocial contingencies. It replaces the term "endogenous depression," which carried the connotation of lack of precipitation, a notion not supported by current evidence. The melancholic cluster is generally believed to predict response to the older class of tricyclic antidepressants and electroconvulsive therapy.

Although decreased sexual desire occurs in both men and women, women are more likely to complain of infrequent menses or cessation of menses. Their unwillingness to participate in lovemaking may lead to marital conflict. Therapists may mistakenly ascribe the depression to the marital conflict, leading to unnecessarily zealous psychotherapeutic attention to the marital situation and a prolongation of the depressive agony. Decrease or loss of libido in men often results in erectile failure, which may prompt endocrinologic or urologic consultation. Again, depression may be ascribed to the sexual dysfunction rather than the reverse, and definitive treatment is often delayed because of the physician's focus on the sexual complaint.

Disturbed appetite and sleep have been described since Hippocrates' classic case (24):

> In Thasos a woman, of a melancholic turn of mind … became affected with loss of sleep, aversion to food … frights … despondency … pains frequent, great and continued.

Most characteristically, there is a diminution in sleep and appetite, but, not uncommonly, one may see an increase or, in rare cases, an alternation between them. Weight gain may be due to overeating, decreased activity, or both. Profound *weight changes* secondary to depression can have serious consequences. Inanition, especially in the elderly, can lead to malnutrition and electrolyte disturbances that represent medical emergencies, often requiring electroconvulsive therapy. Weight gain in middle-aged

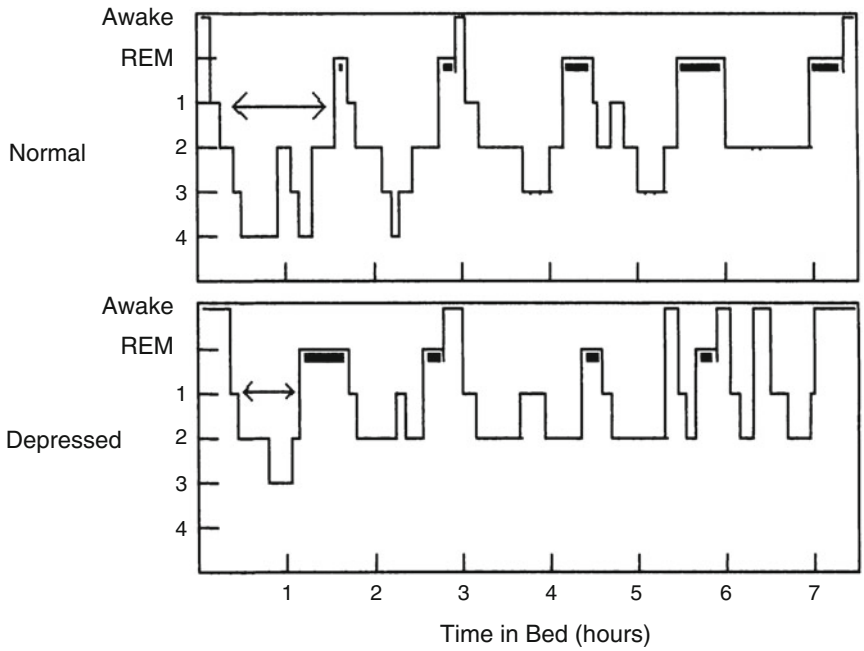

FIGURE 23.1. The sleep histogram of a normal and a clinically depressed individual.

patients, on the other hand, may aggravate preexisting diabetes, hypertension, or coronary artery disease. In younger patients, especially women, weight problems may conform to a bulimic pattern. This could represent the expression of the depressive phase of a bipolar disorder (25) (with infrequent hypomanic periods and/or cyclothymia) and may, therefore, benefit from specific therapies available for this disorder.

Like appetite, sleep may be increased or decreased. *Insomnia* is one of the major manifestations of depressive illness and is characterized more by multiple awakenings, especially in the early hours of the morning, than by difficulty falling asleep. This was described in "Waking up in the Blue," a verse by the American poet Robert Lowell, who had a documented history of bipolar swings (26). The "light" sleep of the depressive is a reflection of the painful arousal and prolongs the agony of the patient. Deep stages of sleep (3, 4) are either decreased or deficient. The understandable attempt to drown the sorrow in alcohol, as the poet Lowell did, may initially have some success but ultimately leads to an aggravation of the insomnia. The same applies to sedative-hypnotic drugs, which are often prescribed by the busy medical practitioner who has not spent adequate time to diagnose the depressive condition. (Sedatives, including alcohol, although effective in reducing the number of awakenings in the short term, are not effective in the long run because of a further diminution of stage 3 and 4 sleep.)

Young depressives, especially those with bipolar tendencies, typically complain of *hypersomnia*, sleeping as long as 12–15 hours a day. Obviously, such patients will have difficulty getting up in the morning; this may lead to their being labeled "lazy." Whether suffering from insomnia or hypersomnia, nearly two-thirds of melancholic patients exhibit a shortening of rapid eye movement (REM) latency, the period from the onset of sleep to the first REM period (27). This abnormality is seen throughout the depressive episode and, in recurrent depressives, may be seen in relatively euthymic periods as well. Other REM abnormalities include longer REM periods and increased density of eye movements in the first half of the night. These abnormalities in REM sleep are rather specific to primary depressive disorders in that they do not occur in most schizophrenic, anxious, and personality-disordered subjects. Figure 23.1 contrasts the sleep electroencephalogram (EEG) of a major depressive with insomnia with that of a normal control.

Other circadian abnormalities in depression include feeling worse in the morning (diurnality), periodicity of episodes, and seasonal precipitation (28). The last two abnormalities are more typically associated with bipolar II disorder. As with other vegetative abnormalities, these, too, point to the limbic-diencephalic dysfunction as the pathophysiologic substrate of the illness. Abnormal response to the dexamethasone suppression test (DST) (i.e., early escape from suppression of elevated plasma cortisol on overnight dexamethasone), seen in 50% of melancholic patients (29), can be considered another indirect indicator of disturbed midbrain function.

In summary, vegetative dysfunction in depressive illness has lent itself to laboratory evaluation that has opened windows into the midbrain origins of the disorder. The sleep EEG and neuroendocrine abnormalities in depression, irrespective of their

etiologic significance, are among the most replicated biologic findings in all of psychiatry and herald psychiatry's new momentum as a medical specialty. Along these lines, the hypercortisolemia in acute clinical depression is often associated with state-dependent enlargement of the adrenals, visible in an abdominal CT scan (30).

23.2.3. Psychomotor Disturbances

Depressed patients exhibit characteristic abnormalities in the execution of motor functions in relation to psychological tasks. Although *agitation* (pressured speech, restlessness, wringing of hands, and, in the extreme, pulling of one's hair) is the more commonly described abnormality, it is less specific to the illness than *retardation* (slowing of psychomotor activity). Indeed, such slowing often coexists with agitation. Psychomotor retardation underlies many of the psychiatric deficits seen in depression: according to research at the Salpêtrière Hospital in Paris (31), psychomotor slowing is manifested by the following disturbances:

- Paucity of spontaneous movements.
- Slumped posture with downcast gaze.
- Overwhelming fatigue—patients complain that "everything is an effort".
- Reduced flow and amplitude of speech and increased latency of responses—often giving rise to monosyllabic speech.
- Subjective feeling that time is passing slowly or has actually stopped.
- Poor concentration and forgetfulness.
- Painful rumination—or thinking that dwells on few (usually unpleasant) topics.
- Indecisiveness—inability to make simple decisions.

DSM-IV places greater emphasis on the more easily measurable objective or physical aspects of retardation. For the patient, however, the *subjective sense of slowing* is often the more pervasive and disabling aspect of retardation. This more "psychological" dimension of retardation is not always easy to elicit from patients, and only those with unusually good premorbid verbal skills can provide reliable descriptions, as documented in the following vignette.

> A 47-year-old moderately depressed physics professor gave the following self-report: "I am weary with a 'leaden' feeling. Manual dexterity is diminished—writing legibly seems like an impossible task. What is most disabling, however, is a kind of staring or stoppage of mental functions… I have great difficulty with the retention of facts and especially words. Recall is sluggish, frustrating. The brain feels 'muddled,' thought processes slowed and confused. My mind simply 'cuts off' at times—often in midsentence or midthought. Yet it seems to dwell on painful subjects. I think about how inadequate I am—and I cannot get rid of that idea, it keeps on coming back. In the morning I feel literally paralyzed with inadequacy and indecision.—I cannot even decide which necktie to wear or whether to wear one at all. I seem to lack any sense of direction or purpose. I have such an inertia.—I cannot assert myself, I cannot fight. I do not seem to have any will at all.

It is because of such psychomotor deficits that depressed patients are often unable to continue to work or do so with much diminished efficiency; the household is typically disorganized; and students fail their classes or drop courses. In the elderly, the slowing of mental functions can be so pronounced that the patient may appear "demented" because of memory difficulties, disorientation, and confusion. This clinical picture is known as *depressive* pseudodementia (32) and may respond dramatically to a course of electroconvulsive therapy. Although appropriate neurologic evaluation may sometimes be necessary before instituting such therapy, the differentiation of pseudodementia from dementia can often be accomplished on primarily clinical grounds (Table 23.3). In some instances, a therapeutic trial with an antidepressant that possesses minimal or no anticholinergic side effects may be the only way to arrive at a differential diagnosis. In young depressives, especially bipolars, psychomotor slowing may in the extreme manifest stupor—the patient is unable to participate even in basic biologic functions like feeding oneself. History is the most reliable way to distinguish depressive stupor from its hysterical and schizophrenic counterparts.

Table 23.3. Clinical features useful in differential diagnosis of depressive pseudodementia from primary dementia.

	Pseudodemented depression	Primary dementia
Onset	Acute	Insidious
Past affective episodes	Common	Uncharacteristic episodes
Self-reproach	Yes	Uncharacteristic
Diurnality	Worse in a.m.	Worse at night
Memory deficit	Recent = remote	Recent > remote
Responses	"Don't know"	Near miss
Reaction to failure	Tend to give up	Catastrophic reaction
Practice effects	Can be coached	Consistently poor

Again, electroconvulsive therapy is often lifesaving in such cases, but somatic causes of stupor (e.g., metabolic, neurologic) must first be ruled out by appropriate clinical and laboratory evaluation.

23.2.4. Cognitive Disturbances

The term "cognition" refers to such things as memory, thinking processes, and thought content. In depression, abnormalities in these areas are often secondary to psychomotor disturbances and, for this reason, were described under that heading. In addition to difficulties in concentration and memory, the depressive exhibits a characteristic thought abnormality consisting of negative evaluations of the self, the world, and the future (the Beckian triad) (33). Clinically, these are manifested as:

- Ideas of deprivation and loss.
- Low self-esteem and self-confidence.
- Self-reproach and pathologic guilt.
- Helplessness, hopelessness, and pessimism.
- Recurrent thoughts of death and suicide.

The main characteristic of the depressive's thinking is that he or she views everything in an extremely negative, gloomy light. The self-accusations are typically unjustified or grotesquely blown out of proportion, as in the case of a woman who was tormented by guilt because, on one occasion 20 years previously, she permitted someone other than her fiancé to kiss her on the lips. Some of these symptoms verge on the delusional. For instance, a world-famous artist presented to his physician with the complaint that he was "nothing." In what is termed psychotic depression, negative thinking acquires grossly delusional proportions, being maintained with such conviction that patients are not amenable to change by evidence to the contrary. Thus, severely depressed patients may manifest delusions of worthlessness and sinfulness, reference, and persecution. They believe that they are being singled out for their past "transgressions" and that everyone is aware of these grievous errors. Persecutory ideation in depression is often *prosecutory* and derives from belief in the necessity of punishment for such transgressions. Other depressives believe that they have lost all their means and that their children will starve (delusions of poverty), or that they harbor an occult and "shameful" illness, such as cancer or AIDS (delusions of ill health), or that parts of their bodies are missing (nihilistic delusions). A minority of depressives may have fleeting auditory or visual hallucinations (e.g., accusatory voices or seeing themselves in coffins or graveyards). All these psychotic experiences are considered *mood-congruent* in the sense that they are understandable in light of the prevailing pathologic mood.

Given the fact that the depressives typically find themselves locked in the private hell of their negative thoughts, it is not surprising that 15% of untreated patients give up hope that they will ever be free of such torments and kill themselves. However, they do not do this at the depth of their melancholia.

The author once asked a severely depressed woman if suicide had crossed her mind, to which she replied, "Doctor, I am already dead. I have no existence." Such a patient is unlikely to undertake suicidal action.

It is when psychomotor activity is improving either spontaneously or with antidepressants—yet mood and thinking are still dark—that the patient is most likely to have the requisite energy to undertake the suicidal act. The German psychiatrist Emil Kraepelin had described this at the turn of the 19th century (34). Unfortunately, antidepressants typically improve mood before psychomotor retardation; that is why the recovery period from depression requires vigilance to prevent suicide.

23.3. The Distinction Between Grief and Melancholia

Depression in its full-blown form is sharply demarcated from the ordinary "blues." The patient and his or her family will tell the doctor that the depressed state represents a break from his or her usual self. The sustained nature of the mood disturbance, the often disabling characteristic signs and symptoms in vegetative, psychomotor, and cognitive areas, the tendency for recurrence, and family history for mood disorder serve to distinguish clinical depression from the ordinary disappointments that are part of the fabric of human existence.

It is in deciding whether a given patient is suffering from ordinary grief or has progressed to clinical depression that the doctor will encounter the greater difficulty. Since bereaved individuals manifest many depressive symptoms within the first year, how does one decide whether grief has progressed to melancholia, as it does in about 5% of such individuals? Clayton and associates (35) have suggested the following criteria as a guideline:

- Preoccupation with suicidal ideation does not occur in normal grief except in some men during the first month or so of bereavement.
- Marked psychomotor retardation is not observed in normal grief.

- Although bereaved individuals sometimes experience guilt about having omitted to offer certain services that may have saved the life of the deceased loved one, they typically do not experience the more pathologic form of guilt known as *guilt of commission* (i.e., guilt about having done something "bad" to their loved one).
- *Mummification*, which refers to maintaining the belongings of the deceased person exactly as they were before his or her death, is abnormal and indicative of psychopathology.
- Severe anniversary reaction should, likewise, alert the clinician to the possibility of psychopathology.

Although dexamethasone suppression test and REM latency findings have not been systematically studied in this context, they also might assist, especially when extremely deviant laboratory values are obtained, in the differential diagnostic process. The following vignette on the joint use of clinical and biologic indices in the differential diagnosis of affective syndromes illustrates the features of pathologic grief (36).

> A 75-year-old widow was brought by her daughter because of severe insomnia and loss of interest in daily routines after her husband's death 1 year earlier. She had been agitated for the first 2 months and thereafter "sank into total inactivity—not wanting to get out of bed, not wanting to do anything, not wanting to go out." According to her daughter, she had been married at 21, had four children, and had been a housewife until her husband's death from a heart attack. Past psychiatric history was negative; premorbid adjustment had been characterized by compulsive traits. During the interview, she was dressed in black, appeared moderately slowed, and sobbed intermittently, saying, "I search everywhere for him I don't find him." When asked about life, she said, "Everything I see is black." Although she expressed no interest in food, she did not seem to have lost an appreciable amount of weight. Her DST was 18 dl. The patient declined psychiatric care, stating that she "preferred to join her husband rather than get well." She was too religious to commit suicide, but by refusing treatment, she felt that she would "pine away, to find relief in death and reunion!"

Current clinical experience indicates that antidepressant treatment is often indicated when grief has reached such a clinical threshold (37).

23.4. The Distinction Between Anxiety and Depressive States

Anxiety is a common symptom of depressive illness, and depression is a common complication of anxiety states. Separating these two alternatives on strictly clinical grounds is not always straightforward. Systematic studies in the UK (38) have shown that early morning awakening, psychomotor retardation, self-reproach, hopelessness, and suicidal ideation represent the most solid clinical markers of depression in this differential diagnosis. On follow-up of depressed patients, these manifestations tend to remit, whereas patients with anxiety states continue to exhibit a spectrum of signs and symptoms consisting of marked tension, phobias, panic attacks, vasomotor instability, feelings of unreality, perceptual distortions, as well as paranoid and hypochondriacal ideas. A predominance of such anxiety features antedating the present bout of illness suggests the diagnosis of an anxiety disorder. It must be kept in mind, however, that anxiety disorders seldom make their first appearance after age 40. Therefore, it is best to consider patients who present with marked anxiety features for the first time after age 40 as suffering from major depression and treat them accordingly. The following case, worked out in a sleep disorder center (36), is illustrative.

> A 52-year-old married teacher with unremarkable previous psychiatric history was referred by his internist to rule out sleep apnea. Over the previous 3 weeks, he had begun to awaken several times at night, gasping for air and sweating, with palpitations and intense fear. There was no special dream recall. History revealed that a colleague, to whom the patient was not particularly close, had recently suffered a severe coronary attack and underwent bypass surgery. Additional complaints of the patient included early-morning awakening, feeling tired in the morning, and tension, irritability, and apprehension throughout the day, rendering classroom teaching difficult. Appetite and libido were unchanged. The patient denied subjective depression. During psychiatric interview, his face expressed worry and gloom, and he appeared moderately agitated; he was tormented by the fear that he might die suddenly, although he could not say from what. Curiously, he was unaware of the temporal connection between the serious illness of his friend and the onset of his own distressing symptoms. Family history was unremarkable. The patient had not responded to a 3-week trial of diazepam, 20 mg/day. After drug washout, polysomnographic evaluation ruled out sleep apnea while demonstrating a REM latency of 38 minutes, middle and terminal insomnia with a sleep efficiency of 64 percent. Within 15 days, the patient showed a dramatic response to a sedating antidepressant.

Such anxious-agitated patients represent variants of unipolar depression and, in former classifications, were termed "involutional melancholia." To support the latter diagnosis, the clinician must document the intrusion of irritable-hypomanic symptoms into the depressive episode. In more severe cases, a bipolar mixed state must be considered in the differential diagnosis (39).

Currently, the differential diagnosis of anxiety and depressive states is not fully resolved. Although recurrent (especially retarded) major depressive illness is most certainly a distinct disorder from anxiety states, at least some forms of depression may share a common diathesis with panic disorder (40).

Sleep EEG studies indicate that short REM latency is uncharacteristic of anxiety states, even when complicated by depression (41). Furthermore, arecoline challenge shortens the REM latency in depression but not in anxiety states (42). DST findings

TABLE 23.4. Cross-sectional differentiating clinical features of anxiety and depressive states.

Anxiety	Depression
Hypervigilance	Psychomotor retardation
Severe tension and panic	Severe sadness
Perceived danger	Perceived loss
Phobic avoidance	Loss of interest (anhedonia)
Doubt and uncertainty	Hopelessness, suicidality
Insecurity	Self-depreciation
Performance anxiety	Loss of libido
	Early-morning awakening
	Weight loss

are generally negative in anxiety states (43). However, corticotrophin-releasing factor (CRF) activity appears elevated in both depressive and anxiety states (44). Basal forearm blood flow is elevated in anxiety but not in depressive states (45). By contrast, baseline skin conductance, another psychophysiologic measure, is lowered in depressive states (46). These promising biologic considerations cannot substitute for clinical judgment. Table 23.4 summarizes clinical considerations which the weight of the literature suggests to be most discriminatory between anxiety and depressive states (47).

Further clinical distinction is family history (48). Thus, patients exhibiting anxiety symptoms during a depression have family members with depression and not anxiety disorders; the opposite is true for patients whose primary diagnosis is an anxiety disorder. Those with mixed states, as expected, often have bipolar family history (39).

A final issue in discussing the relationship between anxiety and depressive states is what has been termed *atypical depression* (49). Classically, these were mild, fluctuating outpatient depressions (which sometimes reached full syndromal depth) seen mostly in young women referred from the cardiology service, because of manifestations of autonomic nervous system overactivity. Against this background of somatic anxiety symptoms, which often led to phobias, these patients suffered from initial insomnia (yet slept deeply and too long once they fell asleep), daytime fatigue and lethargy, overeating, and feeling worse in the evening. This differential diagnosis is important, because monoamine oxidase inhibitors (MAOIs) are more likely to be effective in such patients (50). These patients too might have affinity to bipolar II disorder (51). In brief, marked anxiety component in the setting of depression should not be automatically considered "unipolar."

23.5. The Heterogeneity of Dysthymic Disorders

As defined in DSM-IV, dysthymia refers to chronic, low-grade, fluctuating depressions of at least 2 years' duration. Except for the requirement of chronicity, this group of patients is similar to what, in former classifications, was termed "neurotic depression." This is a heterogeneous grouping that subsumes several nosologically unrelated categories (52). Some patients manifesting low-grade fluctuating depression are not suffering from primary mood disorder; their gloom is secondary to other psychiatric conditions, such as anxiety disorders, anorexia nervosa, conversion disorder, sociopathy, and their variants. More commonly, low-grade depression represents the residual phase of incompletely remitted primary major depressions; such residuals are most commonly seen in late-onset unipolar illness (>40 years). There is also an early-onset primary *dysthymia*. It begins insidiously in teenage years, or even in late childhood, in the absence of other psychiatric disorders and pursues an intermittent course. If major depressions are superimposed, the patient returns to the low-grade, intermittent baseline on recovery. Such patients tend to be introverted, self-sacrificing, and self-denigrating. They are habitually brooding, anhedonic, and hypersomnolent; suffer from psychomotor inertia; and tend to feel worse in the morning. REM latency is reduced to less than 70 minutes, and family history can be positive for either unipolar or bipolar disorder. For this reason, such patients may respond to various antidepressants with subtle hypomanic episodes. In brief, this form of dysthymia appears to be a true "subaffective disorder" (i.e., an attenuated clinical expression of primary mood disorder) or, alternatively, cyclothymia minus spontaneous hypomania. The vignette that follows is a self-description given by a 34-year-old nurse of her "depressive self"; it exemplifies the concept of dysthymia as a subaffective disorder:

> Suffering is so much part of me that it defines my personality. This is manifested by a profound sense of inadequacy which is almost physical. I feel as though a stone is suspended from a long chain inside me dangling over a dark bottomless well. I sense the futility of effort – though not where work is concerned, which, over the years, has been the major principle of my life. My suffering is endured in personal isolation. It has never been possible for me to describe to anyone the overwhelming sadness that almost paralyzes me in the mornings. I have never timed the periods of depression, as they seem to come and go irregularly. My appetite is usually unchanged, but I sleep more, sometimes 15 hours per day. These black periods have been my share in life for as long as I can remember. I have never taken medication for them. Onset is insidious, but return to normal mood can come on suddenly, like the snapping of a light switch, and I will be well for a week or so, and if I am lucky,

for several weeks. My mother suffered a mood disorder. I remember days when she would cry for no reason – when I would come home from school to find her still huddled in bed. My aunt said she was "lazy." And then I remember her becoming hyperactive, grandiose, expansive. Her father also suffered periods of depression. So it would seem almost by destiny that 1 have been sentenced to a life of suffering. My major question is why I have been denied the highs that my mother enjoyed so much – even though at such times she gave hell to my father.

This is one of the unresolved questions in the riddle of the mood disorders—why some of the relatives of bipolar individuals suffer from depressive episodes alone and from depressive "personality" developments, as in the case of this patient. As described in a subsequent section of this chapter, in reality, such patients are "pseudo-unipolar" in the sense that they are at risk for pharmacologically mobilized hypomanic periods.

23.6. The Manic Syndrome

As with the depressive syndrome, mania manifests in disturbances in mood, vegetative, psychomotor, and cognitive functions. It has been known for two millennia, with a compelling description provided by Aretaeus of Cappadocia in the first century A.D. (53). Kraepelin's monograph on manic-depressive psychosis is the classic treatise in more modern times (34). The current usage of the term "bipolar disorder" has helped in destigmatization, by self-confessions of celebrities (54), which provide the opportunity to understand how the illness manifests in real-life situations.

Clinical manifestations in mania are often, although not always, opposite in direction from those seen in depression. Mild degrees of mania (hypomania) can be useful in business, leadership roles, and the arts. A powerful literary portrayal of hypomania is provided by Bellow's Herzog (55). Many creative people have had such elevated periods, without necessarily reaching clinical proportions. Others appear to have suffered from psychotic mood swings; for instance, van Gogh (56), who painted almost 200 masterpieces before committing suicide in 1890, wrote the following description in his letters to his brother Theo: "Ideas for my work are coming to me in swarms … continued fever to work … an extraordinary feverish energy … terrible lucidity." In the case of van Gogh, who suffered from extreme lows and highs, the unstable moods could have had epileptic basis (57). Thus, manic-like syndromes may sometimes originate in nonpsychiatric conditions.

Although mania can be symptomatic of several medical conditions or precipitated by catecholaminergic drugs (58), the syndrome most typically develops in those with the familial manic-depressive diathesis. (Symptomatic manias are listed in Table 23.5.) One of the many reasons that mania is considered an illness is that it often leads to personal disaster and tragedy, as it did in the case of van Gogh. Fortunately, current treatments can often attenuate bipolar swings with relatively little appreciable effect on creativity, which may even be enhanced, thanks to freedom from incapacitating mood swings (59). This is not universal, however, and each patient who derives benefits from hypomanic bursts should be considered individually. Such consideration is important because creativity and achievement appear related to temperamental characteristics most affected by lithium salts.

TABLE 23.5. Medical and pharmacologic factors commonly associated with onset of mania.

Medical conditions
Thyrotoxicosis
Systemic lupus erythematosus
Rheumatic chorea
Influenza
St. Louis encephalitis
General paresis (tertiary syphilis)
Huntington's chorea
Multiple sclerosis
Diencephalic and third ventricular tumors
Complex partial seizures (temporal lobe epilepsy)
Stroke
Head trauma
Pharmacologic agents
Corticosteroids
Levodopa
Bromocriptine
Amphetamines
Methylphenidate
Cocaine
Monoamine oxidase inhibitors
Antidepressants

23.6.1. Mood Change

The mood in mania is classically one of *elation*, euphoria, and jubilation, often associated with laughing, punning, and gesturing. The mood is not stable, and momentary tearfulness is not uncommon. Also, for many patients, the high is so excessive that it is dysphoric. When crossed, the patient can become extremely *irritable* and hostile. Thus, *lability* is as much a feature of the manic's mood as the mood elevation.

23.6.2. Vegetative Disturbances

The cardinal sign here is *hyposomnia*, decreased amount of sleep, the patient needing only a few hours of sleep and feeling energetic on awakening. Some patients may go without sleep for 48 hours at a time and feel even more energetic.

There does not seem to be a primary disturbance of appetite as such, but weight loss may occur because of increased activity and inattention to nutritional needs. The *sexual appetite is increased* and may lead to much sexual indiscretion. Married women with previously unblemished sexual histories may associate with men below their social station. Men may overindulge in alcohol and sex, frequenting bars and brothels where they squander their savings. The sexual misadventures of manic patients characteristically result in marital disasters and multiple separations or divorces. The poor judgment and the impulsivity leading to such behavior are particularly problematic in the era of AIDS and dictate early diagnosis and treatment (62).

23.6.3. Psychomotor Disturbances

Increased psychomotor activity, the hallmark of mania, is characterized by *increased energy and activity* level and by *rapid and pressured speech*. These are coupled with a subjective sense of physical well-being known as "eutonia" and by *flight of ideas*; thinking and perception are unusually sharp or brilliant. Sometimes the patient speaks with such pressure that it is difficult to follow his or her associations, termed "clang associations," often based on rhyming or chance perceptions and flow with great rapidity.

Manic patients are typically disinhibited and meddlesome. They are intrusive in their increased involvement with people, leading to much friction with colleagues, friends, and family. They are *distractible* and quickly move not only from one thought to another but also from one person to another, showing heightened interest in every new activity that strikes their fancy. They are indefatigable and engage in various and sundry activities, in which they usually display poor social judgment. Examples include preaching or dancing in the streets; abuse of long-distance calling; buying new cars, hundreds of records, expensive jewelry, or other unnecessary items; engaging in risky business ventures; gambling; and sudden trips. Obviously, these pursuits can lead to personal and financial ruin. In severe mania, known as "delirious mania," frenzied physical activity continues unabated, leading to a medical emergency requiring daily electroconvulsive therapy.

23.6.4. Cognitive Disturbances

The manic has an *inflated self-esteem* and a *grandiose sense of confidence* and achievements. Underneath this facade, however, the patient sometimes has a painful recognition that these positive self-concepts do not represent reality. Such insight, if present at all, is, unfortunately, transient. Indeed, manic patients are notoriously refractory to self-examination and insight. As a result, manic delusions are often maintained with extraordinary fervor. These include delusions of exceptional mental and physical fitness; exceptional talent; wealth, aristocratic ancestry, or other grandiose identity; assistance (i.e., well-placed people or supernatural powers are assisting in their endeavors); or reference and persecution (i.e., enemies are observing them or following them out of jealousy).

23.7. The Distinction Between Bipolar and Schizophrenic Psychoses

As documented elsewhere in greater depth (56), in depressive psychoses, fleeting auditory or visual hallucinations involving mood-congruent precepts can be experienced in a sizable minority of manic patients. Furthermore, severely ill manic patients can exhibit such a degree of psychotic disorganization that mood-incongruent symptoms pervade the clinical picture, and *cross-sectionally*, it may prove difficult to distinguish them from schizophrenic patients. They may even exhibit isolated Schneiderian symptoms, although this is typically fleeting and occurs at the height or depth of affective psychosis (60). Thinking may be so rapid that it may

appear "loosened," but unlike schizophrenia, this will be in the setting of expansive and elated affect. By contrast, the severely retarded bipolar depressive, whose affect may superficially seem flat, will almost never exhibit major fragmentation of thought. The clinician should therefore consider the clustering of symptoms—rather than individual symptoms—in the differential diagnosis of affective and schizophrenic psychoses. Because the two psychotic conditions entail different therapeutic regimens on a long-term basis, this differential diagnosis (Table 23.6) is of clinical import.

As documented in the UK-US diagnostic project, in the past, many bipolar patients (61), especially those with prominent manic features at onset, were considered "acute schizophrenics" or "schizoaffective schizophrenics." As stated, this often resulted from exclusive reliance on the cross-sectional clinical picture. Although modern treatments tend to keep many schizophrenic patients out of the hospital, the illness still pursues a downhill course; by contrast, the inter-morbid periods in bipolar illness are characterized by temperamental oscillations that can be dysthymic, hyperthymic, or cyclothymic; in a selected few, the inter-episodic periods are marked by supernormal functioning, although in other patients some social impairment may come, over time, from the accumulation of divorces, financial catastrophes, and ruined careers. Genetic studies tend to separate the two disorders; e.g., discordance in identical twins for schizophrenia and bipolar illness is rarely due to the presence of the other disorder. Laboratory markers have not yet been systematically applied in the two disorders in the clinical setting; it is of clinical interest, however, that thyroid-stimulating hormone (TSH) blunting in response to thyrotropin-releasing hormone (TRH) challenge is almost never positive in schizophrenia, at least not in chronic schizophrenia (62).

Schizoaffective (or cycloid) psychosis refers to an uncommon form of recurrent psychosis with full affective and schizophrenic symptoms during each episode (63). Such a diagnosis should not be considered in an affective psychosis where mood-incongruent psychotic features (e.g., Schneiderian and Bleulerian symptoms) can be explained on the basis of one of the following (64): (1) affective psychosis superimposed on mental retardation, giving rise to extremely hyperactive and bizarre manic behavior; (2) affective psychosis complicated by concurrent medical or neurologic diseases, substance abuse, or withdrawal, giving rise to numerous Schneiderian symptoms; or (3) mixed episodes of bipolar illness, which are notorious for signs and symptoms of psychotic disorganization.

Although mixed features (i.e., crying while manic) commonly occur in the course of bipolar disorder, mixed states with the full complement of depressive and manic syndromes occur in nearly 40% of bipolar patients (65), who exhibit the following signs and symptoms: crying, euphoria, racing thoughts, grandiosity, hypersexuality, suicidal ideation, irritability, anger, psychomotor agitation, severe insomnia, persecutory delusions, auditory hallucinations, and confusion. Such an episode, if it is the patient's first psychotic break (65, 76), can be extremely difficult to characterize diagnostically unless it is immediately followed by more typical retarded depressive or manic episodes or family history is positive for bipolar illness. The following vignette (reprinted from Ref. (64) exemplifies these points.

> A 19-year-old boy was admitted to a state psychiatric facility because of social withdrawal, insomnia, severe headaches, and the obsession of sticking a knife into his heart in order to punish himself for rape fantasies. While in the hospital, he heard the devil's voice telling him that he should hang himself before a misfortune killed his entire family. His mood was extremely labile; his mental status shifted to an irritable-cantankerous mood; he expressed thoughts of cutting someone's cheeks with a knife (which he eventually did); he entered women's lavatories and said he could "seduce all of them at once;" he started communicating with God (but he wouldn't say how) and expressed the idea that his biologic father was Jesus Christ. At this juncture, he was physically accelerated, spoke constantly, did not experience any need for sleep, flirted with the nurses, joked with everybody, and danced naked in front of other patients "to aid in a campaign to help the Poor." On full remission on lithium carbonate, he expressed great guilt over his aggressive behavior during the intermediate mixed state of transition from depression into mania; as a matter of fact, he donated all of his savings to aid his victim in recovering from cosmetic surgery.

TABLE 23.6. Clinical features distinguishing bipolar from schizophrenic psychoses.

	Bipolar disorder	Schizophrenia
Cross-sectional		
Affect	"Contagious"	"Praecox feeling"
Thought	Accelerated or retarded	Poverty of content and bizarre
Autism	Uncharacteristic	Characteristic
Hallucinations	Fleeting	Intermittent or continuous
First-rank symptoms	Few (<2)	Numerous
Longitudinal		
Premorbid	Cyclothymic	Schizotypal
Inter-morbid	Tempestuous, "supernormal"	Withdrawn or low functioning
Course	Biphasic	Fluctuating, downhill

As alluded to earlier in the section on depression, a subacute mixed state (i.e., one without psychotic features) can be confused with a severe anxiety state. Accurate diagnosis is essential, since mixed states tend to be notoriously refractory to antidepressants and lithium may work too slowly, if at all. Electroconvulsive therapy is usually the more definitive treatment. Newer anticonvulsant and atypical antipsychotic treatments can often substitute for ECT.

23.8. Hypomania and Its Diagnostic Significance

Setting the threshold for clinically significant hypomania is not only important for differentiating normal merriment and creative moods from illness but also for diagnosing bipolar II disorder. The following criteria, developed at the University of Tennessee Mood Clinic (66), may assist in setting the clinical threshold for hypomania:

- It is often dysphoric in its drivenness.
- It is labile; i.e., the elation is unstable and easily alternates with irritability and anger.
- It may lead to substance abuse as a means to control the experienced high.
- It may impair social judgment, even if the patient appears to be behaving "rationally."
- It is preceded or followed by retarded depression, typically with abrupt transition.
- It often springs from familial background of bipolar disorder.

Hypomania is a recurrent condition, forming part of several overlapping "soft" bipolar subtypes (see Table 23.1) of which *bipolar II* disorder is the most common. Bipolar II patients who seek psychiatric help are usually women in their 20s and 30s who have suffered recurrent bouts of retarded depression. Because their highs are short-lived and typically not perceived as disruptive—indeed, the patient often finds them enjoyable—these individuals seldom present for help during such periods. The illness usually begins in the mid or late teens and leads to much interpersonal chaos. This facet of the illness can so impress the clinician that he or she may embark on a long-term psychotherapeutic endeavor, when in reality the tempestuous biography represents a complication of the recurrent mood disorder. It is therefore critical to document hypomanic swings in such patients in order to bring them the benefit of mood-stabilizing medications. Another reason why accurate early diagnosis is important here lies in the fact that the continued antidepressant use in such patients may not only precipitate hypomanic and mixed periods but also tend to lead to increased cycling in the long term (67). Cycles refer to the period from the onset of one episode to that of a subsequent one. In so-called rapid-cycling patients, who often come from the rank of bipolar II disorder, cycle frequency increases to at least four per year (68). The vignette that follows describes the subtle nature of the hypomanic periods in bipolar II patients and the ease of its induction by antidepressant pharmacotherapy.

> A 26-year-old medical secretary who was separated from her third husband presented for outpatient psychiatric care with the chief complaint of "lack of hope, joy, meaning, and focus in life." She said she lacked the energy and motivation to take care of daily routines and slept 12 to 14 hours nightly. She said she would rather die than go through another divorce. She could not concentrate at work, and her typing speed had deteriorated. Since her teens she had had numerous similar periods that lasted from 2 to 12 weeks. These episodes often terminated abruptly, at which time she felt such an "intense relief and joy that I would sleep with the first man who happened to be around." It is this behavior that has led to repeated marital conflict and intermittent psychotherapy with little tangible benefit. On further questioning, she revealed that during the sudden recovery period, which lasted 2–3 days, she sometimes felt no need for sleep, felt such "ecstasy from being alive again that I would cry," and had to drink whiskey to be able to "calm down my mind and body galloping with new life." Her husbands and numerous lovers were often irritated by her increased zeal, which led to new sexual misadventures. Family history revealed that a maternal uncle who had never received psychiatric help but who was known to be an alcoholic had hanged himself in his early 40s. An older sister had been treated for "mild depressions." Their mother had been periodically treated for excited psychotic states that had been labeled "paranoid schizophrenia," but little evidence could be found to substantiate that diagnosis; she had been married five times, indulged in much gambling and associated with people in art circles. Given that the mother's illness suggested mania, and given the abundance of historical evidence for hypomanic episodes in the patient, lithium carbonate was recommended. The patient refused to consider this treatment. Ten days later she was seen in the emergency department in an accelerated state and complained that she had not slept for two nights; she also revealed that she had been taking her sister's "tranquilizer," which turned out to be antidepressant tablets.

Cyclothymic disorder often presents clinically in a similar fashion, except that the depressive periods are shorter, lasting for just a few days rather than for weeks, and are not of full syndromal depth. These rapid and tempestuous mood swings render the differential diagnosis from personality disorder somewhat problematic (69). Table 23.7 summarizes the main features of cyclothymia that need to be taken into account in such differential diagnosis. Cyclothymia may also serve as the baseline of manic-depressive episodes, and this pattern is considered *bipolar II-½* (i.e., between BP-II and BP-III).

TABLE 23.7. Clinical features of cyclothymic disorder.

General characteristics
Onset before 21 years
Short cycles (days), which are recurrent in an irregular fashion, with infrequent euthymia
May not attain full syndrome for depression and hypomania during any one cycle, but entire range of affective symptoms occur at various times
Abrupt and unpredictable mood change
Subjective symptoms
Lethargy alternating with eutonia
Pessimism and brooding alternating with optimism and carefree attitudes
Mental confusion and apathy alternating with sharpened and creative thinking
Shaky self-esteem alternating between low self-confidence and grandiose overconfidence
Behavioral signs
Hypersomnia alternating with decreased need for sleep
Introverted self-absorption alternating with uninhibited people-seeking
Taciturn versus talkative behavior
Unexplained tearfulness alternating with excessive punning and jocularity

In still another variant of the bipolar spectrum known as *bipolar III*, the patient suffers from early-onset repeated bouts of retarded depression which can be either major episodes or intermittent minor depressions with the pattern of subaffective dysthymia as described earlier, but without evidence for spontaneous hypomanic periods; the bipolar tendency in these patients becomes manifest on pharmacologic challenge with antidepressants. Family history is often positive for frank bipolar illness (70). These pseudo-unipolar patients, who are sometimes referred to as unipolar II, represent either a less penetrant genetic form of bipolar disorder or simply the earliest depressive beginnings of bipolar disorder. The question then becomes, can one predict which depressives will eventually switch into bipolar disorder? The following clinical features have been found useful in this regard in prospective follow-up studies (6, 71):

- Onset before age 25.
- Abrupt onset and offset.
- Psychotic depression in a teenager; abrupt onset.
- Postpartum onset.
- Hypersomnic-retarded depression.
- Pharmacologic mobilization of hypomania.
- Bipolar family history.
- Loaded (especially three consecutive generations) family history for mood disorder.

This section on the milder end of the bipolar spectrum would be incomplete without mentioning chronically or intermittently hypomanic individuals termed hypomanic personality or *hyperthymic temperament* (72). This condition is characterized by intermittent subsyndromal hypomanic features with infrequent intervening euthymia. They are typically short sleepers (4–6 hours per night) and are high achievers. Although irritability is often seen in these individuals, depression as such is extremely uncommon; in other words, hyperthymia can be described as cyclothymia with the minimum amount of depression, characterized by excessive use of denial, and given their successes in leadership positions or business, such individuals, unless suffering from a superimposed major depression, rarely present for psychiatric treatment. They are more often seen in sleep disorders centers, where they seek help because of sleep difficulty.

23.9. Mood Disorder in Different Clinical Settings

This chapter has presented the manifold clinical picture of mood disorders that embrace a broad range of somatic, psychomotor, emotional, and cognitive manifestations, as well as certain interpersonal and social disturbances representing complications of the illness. For this reason, the differential diagnosis of affective signs and symptoms interfaces with the "blues," bereavement reactions, anxiety states, primary character disorders, substance use disorders, schizophrenia, and dementia. Furthermore, depending on the clinical setting, one set of manifestations may dominate the clinical presentation. Common examples include the following:

- Primary care: somatic complaints and substance abuse.
- Sleep disorder center: insomnia and hypersomnia.
- Urology: impotence.

- Neurology: memory disturbances.
- Emergency department: psychosis and suicide attempts.
- Educational counseling: scholastic failure.
- Psychology and social work: marital problems.
- Psychoanalysis: character pathology.
- Courts: violence and murder.
- City morgue: suicide.

Since primary mood disorders are eminently treatable disorders—and because the complications of untreated depression or mania can be extremely serious—all physicians, as well as mental health professionals, should be competent in determining whether a given set of affectively tinged signs or symptoms are due to a primary mood disorder. The clinician should always inquire:

- Are unexplained somatic complaints and substance abuse alternative expressions of a primary mood disorder?
- Are insomnia and hypersomnia part of an affective syndrome, acute or chronic?
- Did depression precede the impotence?
- Are memory disturbances secondary to a reversible melancholia?
- Despite "schizophrenic" coloring, is the psychosis one phase of a recurrent bipolar disorder?
- Is school failure in a teenager or a young adult caused by a retarded depression heralding the onset of a bipolar disorder?
- Are marital problems secondary to depression, cyclothymia, or frank bipolar disorder in one or both spouses?
- What appears to be borderline character pathology: is it due to a cyclothymic or related temperament?
- Was the violent act committed during a psychotic depression or manic excitement?

It is necessary to inquire along these lines because it is obviously too late to do so in the city morgue! Mood disorders are serious clinical issues and necessitate a systematic approach to determine the affective basis of a patient's presenting complaints in different settings:

- To elicit other clinical features of the affective syndrome under consideration.
- To document history of more typical major affective episodes in the past.
- To assess if the presenting complaints recur in a periodic or cyclic fashion.
- To substantiate relatively good social functioning between periods of illness.
- To obtain positive family history for mood disorder and construct a family pedigree.
- To document an unequivocal therapeutic response to thymoleptic agents or electroconvulsive therapy.

In summary, the physician or mental health worker who engages in a systematic differential diagnosis of affective disturbances will soon find that many clinical enigmas will be solved in favor of a primary affective diagnosis. Because mood disorders are the most common and treatable of the serious psychiatric disorders, the practitioner is statistically admonished to err on the side of such diagnosis.

To avoid diagnostic errors, the physician must be well grounded in classical psychopathology. Good modern sources on the psychopathology of mood disorders include Beck's *Depression* (33), Maj et al.'s *Bipolar Disorder* (73), Taylor and Fink's *Melancholia* (74) and Goodwin and Jamison's *Manic-Depressive Illness* (75), and the Marneros-Akiskal monograph (76). The impact of affective temperaments in the origin and course of mood disorders has been recently published in a special issue of the *Journal of Affective Disorders* (77). Validated self-rated temperament measures can also be found in that special issue.

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24
Anxiety Symptoms

Charles Van Valkenburg, M.D.

Abstract Anxiety symptoms are common and distressing, and range in severity from mild and adaptive to transcendentally severe and disabling. Anxiety symptoms are caused by and comorbid with many medical and psychiatric illnesses. Anxiety diagnoses/symptoms virtually always make the comorbid illness more severe and disabling, more difficult to treat, and make the prognosis worse.

Keywords Anxiety • Panic • Generalized • Phobia • Posttraumatic • Comorbidity

24.1. Introduction

Anxiety diagnoses are coming increasingly into question, but it is anxiety symptoms that we treat. Many anxiety *symptoms* are distinctive. One of the most specific is the panic attack. The anxiety symptoms most likely to come to medical attention are those of panic attacks: spells of intense anxiety, usually sudden and unexpected, lasting a few minutes or hours. Anxiety can be so intense that patients describe it as worse than the worst anxiety they could possibly have; a transcendental, unreal experience. Many who have visited emergency departments during previous attacks without satisfaction feel compelled to do so again. They feel that something horrible is about to happen, that they are doomed. Their surroundings seem changed, menacing. They fear they will lose control of their bodies, perhaps urinating or defecating in front of everyone, perhaps fainting, killing babies, or humiliating themselves irremediably. They feel they are losing their minds, going crazy. They may feel their bodies have become distorted, no longer theirs, or that they are floating outside their bodies. They feel their hearts pounding and feel they cannot get air despite hyperventilating. They sometimes feel a lump or constriction in the throat is choking them. Their chests feel heavy, uncomfortable, painful. They feel waves of numbness or tingling in their arms and legs, or around their mouths. They might feel an electric shock has jolted through their bodies, or feel hot or cold flashes. They feel as if they will faint, and experience dizziness, unsteadiness, perspiration, weakness and tremulousness. Some feel the need to escape from wherever they are. Others feel immobilized. Not all patients have all the symptoms. Sometimes the physical symptoms are present but the fear is missing (1, 2).

Over the centuries, this syndrome, has been called anxiety hysteria or *globus hystericus* (3), neurasthenia, or nervous exhaustion (4), ataque de nervios (5), irritable heart, soldier's heart, or Da Costa's syndrome (6), anxiety neurosis (7, 8), the hyperventilation syndrome (9), the calamity syndrome (10), the phobic anxiety-depersonalization syndrome (11), spasmophilie (12), endogenous anxiety (13), and finally panic disorder (14–16). Most newer names have represented delineations of ever more discrete syndromes from earlier, broader categories.

Almost a quarter of Americans have had a panic attack. Panic disorder without agoraphobia is diagnosed in 3.7%; panic disorder with agoraphobia in 1.1% (17). Severity of anxiety seriously interferes with work productivity (18). They experience a diminished quality of life (19). Because of these comorbid conditions, patients with panic attacks are at increased risk

C. Van Valkenburg, M.D. (✉)
Alabama Clinics, 2812 Hartford Highway, Suite 1, Dothan, AL 36305, USA
e-mail: cmvvmd@gmail.com

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for suicide attempts (20). Susceptibility appears to be genetically (21, 22) and epigenetically transmitted (23), and influenced by adverse life events such as being abused (24), molested (25), raped (26), bullied (27), or teased (28).

Panic attacks are often comorbid with medical illnesses, especially with respiratory disorders, (29–39), vestibular dysfunction (40), hyperthyroidism and hypothyroidism (41–44), cardiac disorders (45–50), hypertension (51, 52), migraine (53), and, seizure disorder (54–58). Feelings of panic are highly associated with hyperdynamic adrenergic activity (59–61). Patients who experience panic attacks typically go to primary care specialists first (62). Those whose syndromes seem inadequately explained by physical findings, may be referred to psychiatrists, particularly if their symptoms do not respond to timid doses of benzodiazepines.

24.2. Organic Anxiety Syndromes: Anxiety Syndromes Associated with Medical Conditions

Apart from anxiety, depersonalization and derealization, most panic symptoms are physical. Some panic attacks consist of physical symptoms without anxiety (1, 2). Most patients with panic attacks initially believe they have physical illness. This is not an implausible assumption, considering the many physical illnesses which can cause such symptoms. Before categorizing symptoms as psychiatric, it must first be determined that physical illness is not their sole cause. But even when a physical illness can be objectively diagnosed, comorbid anxiety will seriously influence severity and outcome.

24.2.1. Cardiac Diseases

24.2.1.1. Myocardial Infarction

The usual predominant symptom of a heart attack is crushing chest pain. Shortness of breath, choking or smothering sensations, palpitations, heavy perspiration and a feeling of impending death are secondary symptoms. Some heart attack patients experience out-of-body experiences and other forms of depersonalization or derealization. Many will have had previous attacks. Mild heart attacks could be misdiagnosed as panic attacks.

Fortunately, there are good diagnostic tests for heart attack. An electrocardiogram (EKG) can quickly establish the correct diagnosis, and assays of cardiac enzymes in the blood confirm it. Most clinicians and even untrained persons can recognize a serious heart attack. Anxiety symptoms often co-occur with myocardial infarction, and lead to a worse prognosis (48). Typically anxiety is closely attended to, monitored and treated in the aftermath of a heart attack, in attempts to reduce the risk of death over following days and years.

24.2.1.2. Angina Pectoris

Angina pectoris is characterized by episodes of chest pain or discomfort, heart palpitations, shortness of breath, trouble breathing, and, understandably, anxiety. The episodes are often precipitated by exertion, or by typical anxiety-provoking stimuli, or can appear to be spontaneous

The symptomatic overlap of angina and anxiety remains considerable. Both are relatively common, and an individual patient might have both diseases. The diagnostic distinction between angina pectoris and panic remains difficult for cardiologists (31, 63). Cardiologic findings take precedence. But the psychiatric contribution is not trivial.

Benzodiazepines have proven useful in the management of angina and even silent ischemia (63). Anxiety symptoms should be treated in patients with chest pain, whether or not there is objective evidence of coronary artery disease. SSRI drugs slowly reduce anxiety and are safe for the heart, but several, including fluoxetine and paroxetine, can seriously interfere with the metabolism of warfarin, used for anticoagulation. Citalopram and sertraline do not have this problem.

24.2.1.3. Heart failure

Heart failure is highly comorbid with anxiety and mood disorders (62). Cardiomyopathy no longer stands out as worse than other heart failure.

24.2.1.4. Mitral Valve Prolapse Syndrome

Mitral valve prolapse syndrome can cause panic attacks indistinguishable from panic disorder. But most patients with mitral valve prolapse have no particular anxiety symptoms.

24.2.1.5. Cardiac Dysrhythmias

Cardiac dysrhythmias can cause palpitations, chest pain or discomfort, dizziness, respiratory distress, fainting, and anxiety (64). Patients with panic disorder often have dysrhythmias, including premature ventricular contractions. Not all dysrhythmias cause subjective symptoms, and not all dysrhythmia symptoms coincide with pulse and EKG changes.

Episodes of Paroxysmal atrial tachycardia (PAT) can be mistaken for panic attacks. Measured pulse rates in panic attacks are often normal (65) and seldom exceed 120. In contrast, PAT typically causes a pulse rate above 150. Fortunately, most dysrhythmias can be documented and characterized by EKG. Dysrhythmias can cause anxiety symptoms which might or might not resolve entirely with antiarrhythmic treatment.

Comorbid anxiety symptoms can be treated with selective serotonin reuptake inhibitors, which are generally safe for the heart. Benzodiazepines have little effect on heart rhythm, but can suppress respiration. Panic attacks cannot be dismissed as trivial and not worth the risk of treating in dysrhythmia patients, but neither should anxiety be treated without regard to potentially life-threatening side effects.

24.2.2. Respiratory Diseases

Respiratory symptoms are a central part of panic disorder. Patients with panic tend to hyperventilate slightly between attacks (66).

24.2.2.1. Pulmonary Emboli

Small bits of clotted blood or debris released into the bloodstream usually come to rest in the lung. If a large enough area of blood flow is interrupted, impaired respiration results in shortness of breath, hyperventilation, and acute anxiety.

Listening to the lungs will sometimes suggest pulmonary embolism, but in many cases there are no physical findings. A chest X-ray might not help either. Arterial blood gasses might show decreased oxygen. Lung scan and pulmonary arteriogram can establish the diagnosis definitively, or can miss it. Recurrent pulmonary emboli are expected mainly in individuals with predisposing conditions, such as phlebitis or intravenous drug abuse.

24.2.2.2. Asthma

Like panic disorder, asthma is characterized by episodic attacks of cardiopulmonary symptoms and anxiety. There is a high comorbidity of asthma and panic disorder (68–70).

Patients who say they have asthma or who are being treated for asthma have an increased incidence of panic attacks (67–69). Anxiety disorders increase the history of tobacco smoking and anxious patients are more likely to report allergies (70): both of these risk factors for asthma are contributors to the association. Allergies also increase the reporting of anxiety, without regard to asthma. Treatment of the allergy decreases the anxiety (71).

Anxiety can precipitate and prolong asthma attacks (72). Panic disorder and asthma are highly associated, and the presence of panic attacks makes asthma's course and outcome worse, and treatment more difficult (72). Management of anxiety is a part of treating asthma. Theophylline, used to treat asthma, can cause or exacerbate panic anxiety. Benzodiazepines can suppress respiration in asthmatics. This is a concern but not a contraindication. The SSRI drugs are preferred on theoretical grounds because they do not suppress breathing. Most patients express preference for the benzodiazepines.

24.2.2.3. Chronic Obstructive Pulmonary Disease (COPD)

Generalized anxiety and panic disorders, along with depression, are comorbid with COPD in as many as half of cases (73, 74). Comorbid anxiety significantly diminishes the quality of life of these patients (74). It is important to assess these patients with respect to anxiety and mood disorders. The SSRI drugs are probably the safest treatment (75). "White coat hypertension" (76) is blood pressure elevated by the stressful situation of being in the clinic. More accurate blood pressures can often be gotten later in the clinic visit, or by the patients' self-measurement at home. But 'white coat' hypertension tends to progress to the general kind.

24.2.3. Neurologic Diseases

24.2.3.1. Seizure Disorders

"Anxiety, panic attacks, and pseudoseizures may resemble complex partial seizures, and their diagnosis and treatment may be confusing (77)." Seizure disorders can cause any psychiatric symptom, including any anxiety symptom (78). Some temporal lobe seizures do not progress to generalized convulsions, but present as episodes of anxiety, anger, or other affects (79, 80). Williams (81) found fearfulness to be the predominant emotion in 61% of patients with partial complex seizures. Panic disorder comorbidity is increased by ictal fear (82).

24.2.3.2. Transient Ischemic Attacks

Transient ischemic attacks (TIAs) include transient neurologic signs similar to those of stroke. Anxiety is often part of these episodes and may occur in discrete episodes or attacks for weeks or months before characteristic neurologic symptoms begin to appear. The attacks are caused by episodic arterial insufficiency, most often of the internal carotid or less often of the basilar artery. Patients with TIAs require prophylactic anticoagulant drugs or surgery. Stroke is a frequent outcome.

24.2.3.3. Huntington's Disease

In a minority of cases, before choreiform movements and flaccid paralysis begin, the prodromal phase of this illness is dominated by panic and anxiety (83).

24.2.3.4. Parkinson's Disease

Panic attacks are common in patients with Parkinson's Disease (84, 85), and may be related to motor block frequency and locus coeruleus dysfunction. Generalized anxiety disorder is increased in dystonias (86).

24.2.3.5. Sleep Disorders

About a fifth of patients with isolated sleep paralysis have comorbid social anxiety disorder, panic disorder, or generalized anxiety disorder. Most panic disorder patients have sleep complaints, especially if they have nocturnal panic attacks. Disturbed sleep is used in the definitions of panic disorder, generalized anxiety disorder and posttraumatic stress disorder (87).

24.2.4. Endocrine Diseases

24.2.4.1. Hyperthyroidism

Like panic disorder, hyperthyroidism is associated with chronic and acute episodic anxiety (88). Thyrotoxicosis causes anxiety, palpitations, perspiration, hot skin, rapid pulse, active reflexes, diarrhea, weight loss, heat intolerance, proptosis and lid lag. Severe cases are easy to recognize clinically. Early or mild cases can be discriminated from anxiety disorders by the serum levels of thyroid hormones. But many anxiety patients also have abnormal thyroid indices, particularly low TSH levels (89). These abnormal thyroid function tests may not reflect true thyroid disease, but feedback from the hypothalamic-pituitary-adrenal (HPA) axis (89).

Little has been written concerning treatment of anxiety in true thyroid disease, but clinical experience suggests our usual psychotropic medications will have little effect, until the hyperthyroidism has been brought under complete control. Sometimes an increase in anti-thyroid therapy is effective even when the serum thyroid indices seem satisfactory to the endocrinologist.

24.2.4.2. Hypoparathyroidism

The symptoms of hypoparathyroidism are those of low serum calcium, and vary considerably. Anxiety is the predominant symptom in 20% of cases. Other typical symptoms include paresthesias, muscle tension and cramps, spasm and tetany. Most cases result from past surgical removal of the parathyroids during thyroidectomy. Diagnosis is suggested by low serum calcium and high phosphate levels, and confirmed by parathormone assay. Any low serum calcium level requires immediate treatment. This should relieve the anxiety along with the other symptoms. Little is written about what to do if it is not. This problem has become rare, and not the subject of recent reports.

24.2.4.3. Hyperparathyroidism

Anxiety can be a presenting symptom of hyperparathyroidism, along with weakness, fatigability, and loss of appetite. However the syndrome is most typically found after routine blood tests show an increased calcium level (90). Parathyroidectomy is the definitive treatment. No study has suggested a role for anxiolytic drugs.

24.2.4.4. Pheochromocytoma

Pheochromocytoma is uncommon but dangerous and treatable, and so must always be borne in mind in the assessment of anxiety symptoms (91). Half of pheochromocytoma patients have acute attacks of anxiety, headache, sweating, flushing and hypertension. Blood pressure is usually elevated between attacks as well. Pheochromocytoma attacks, like panic attacks, can be precipitated by emotional experiences. Pheochromocytoma attacks are more likely to cause crushing back pain, vomiting, and sweating of the whole body; the sweating in panic attacks is more likely to be confined to the hands, feet and forehead. No systematic study has shown any treatment or predictive value of making a separate anxiety diagnosis.

24.2.5. Intoxications

24.2.5.1. Caffeine and the Methylxanthines

Caffeine is a commonly consumed stimulant, and too much of it will provoke anxiety symptoms. While lower doses of caffeine can be pleasantly stimulating, higher doses cause hyperalertness, hypervigilance, motor tension and tremors, gastrointestinal distress, and anxiety. The acute symptoms of caffeine intoxication and generalized anxiety disorder are almost identical. In dosages of around 700 mg, about seven cups of weak American coffee, caffeine will provoke panic attacks in most persons with panic disorder and in many persons without prior panic attacks. Diagnostic evaluation of panic attacks must assess the possibility of caffeine intoxication. Not all of caffeine's effects are reversed by benzodiazepine. Caffeine, theophylline, theobromine and related methylxanthines are found in coffee, tea, cola and many other carbonated drinks, yerba maté, guaraná, and other drinks derived from various plant leaves, fruits and flowers. They are also ingredients in many medications including analgesic combinations, diet pills, and nonprescription stimulants. Theophylline, the methylxanthine that predominates in tea, is prescribed for a variety of respiratory diseases and can cause the same generalized panic and anxiety as caffeine.

Many patients with anxiety disorder have learned to avoid or limit caffeine. Patients who complain of anxiety and report heavy caffeine consumption should be advised to decrease or discontinue caffeine before other treatments are considered. Widely consumed 'energy drinks' typically contain caffeine and are associated with panic and generalized anxiety symptoms (92). Many of these advertise caffeine contents lower than 700 mg, but contain additional ingredients intended to augment the caffeine's effect.

24.2.5.2. Yohimbine

Yohimbine has been used to produce penile erection, but it also can produce extreme anxiety (93). It produces panic and anxiety so reliably that it has been useful in experimental anxiety research. Intoxicated persons will show more overstimulation, irritability, and gastrointestinal distress than is typical of panic attacks. Yohimbine is still used to produce a 'biological challenge' (94) but now seems to be little consumed outside the laboratory. Its toxicity is antagonized by clonidine and diazepam (95).

24.2.5.3. Heavy Metals

Heavy metal poisoning can cause a complex mixture of somatic symptoms and anxiety. "Hatter's Madness" is best documented, and causes symptoms including anxiety, phobic avoidance, tremor, weakness, excessive sweating, decreased attention and agitation.

24.2.5.4. Amphetamines, Cocaine, Stimulant Abuse

Persons who use amphetamines or cocaine expect to become euphoric, energetic, confident and accelerated. But they can become agitated, anxious or panicky, particularly with higher doses or prolonged use. The anxiety can become so severe that abusers will take heroin or even antipsychotic medications to counteract it. Panic and anxiety can also result from occasional

use of cocaine. Regular cocaine use is comorbid with a three-fold or greater risk of panic attacks. The symptoms associated with amphetamine abuse are similar but more severe.

Stimulant toxicity is relatively easy to diagnose: dilated pupils, elevated blood pressure with slowed pulse, headache, dizziness, confusion and aggressiveness suggest it, and a urine or blood test confirms it. The same symptoms can be caused by nonprescription diet pills containing phenylpropanolamine or by decongestants or drinks containing ephedrine or pseudoephedrine.

The amphetamine derivative MDMA 'ecstasy' 'XTC' or 'Molly', can cause anxiety, fear, shortness of breath, nausea, vomiting, bruxism, muscle aches, headaches and numbness. Recent reports have advocated its use in the treatment of PTSD (96), or advocated more caution (97). Investigations in the US have been impeded by MDMA's Schedule I status.

24.2.5.5. Khat, Qat, Catha edulis.

Khat is a botanical stimulant widely chewed in parts of the world. A derivative, meth-khat is easily synthesized from ephedrine in illicit laboratories. Khat contains cathinone and cathine (98) which are considered to be natural amphetamines. Several similar compounds are weaker but must contribute to the overall intoxication. Biology teaches us that a plant would not continue the considerable genetic burden to produce several toxins, if each did not augment the effects of the others. Like other botanical stimulants, Khat can produce extreme anxiety. Its users report it both to cause and to relieve anxiety (99). It is often chewed in situations of armed conflict (100).

24.2.5.6. Bath salts

Semisynthetic drugs not yet specifically outlawed are commonly sold 'not for human consumption' (wink, wink) under innocuous sounding names such as 'bath salts.' Initial reports of analyses often find these predominantly contain laboratory Khat derivatives like mephedrone and MDPV (3,4-methylenedioxypyrovalerone) (101, 102). As is common with new drugs, absolutely horrid reactions are being reported. Drugs purchased illicitly can contain just about anything.

24.2.5.7. Cannabis

Unlike recent designer drugs, cannabis has been with us for a long time. For some persons the depersonalization marijuana often causes is experienced as unpleasant, and provokes anxiety, fearfulness and agoraphobic symptoms (103).

A great number of PTSD patients are reporting that cannabis gives the best relief they get, from PTSD symptoms of anxiety and anger. At the same time, purified THC can be prescribed, and 'medical marijuana' can be prescribed, in some jurisdictions for the relief of anxiety and PTSD. There are a lot more synergistic psychoactive compounds in cannabis than just THC. In a substance abuse setting striving for abstinence in patients who are considered cannabis dependent (104), the anxiety symptoms cannabis use has mitigated, are considered "a pernicious feedback loop between PTSD symptomatology and cannabis use." The same issue would be found in opioid abusers between their drug abuse and their pain. 'Authorized' cannabis relieves the same symptoms as unauthorized (105), especially insomnia, pain, and anxiety. It has been hypothesized that the benefits of cannabis in PTSD might derive from its potentiation of fear extinction (106). Cannabis will be with us to study. Self-medication will lead the way.

Recently 'synthetic cannabinoid products' have increased in availability and use. These typically are added to non-cannabis leaves and smoked. They are associated with a high incidence of adverse effects, including anxiety (107).

24.2.5.8. LSD and Psychedelics

Lysergic acid diethylamide's risk of producing "bad trips" is legendary. These are often associated with severe anxiety, as anyone who has ever covered an emergency room near a rock concert can attest. The effects of LSD are typically abolished within an hour by 50 mg of chlorpromazine, given intramuscularly (108). Contrary to the old street lore, this use of chlorpromazine is usually quite safe. Past use of psychedelics is associated with some *decrease* in current mental health problems (109).

24.2.5.9. Nitrites

Amyl nitrite is used medically as a short-acting vasodilator. It is abused primarily as a sexual stimulant, for prolonging and intensifying arousal, erection and orgasm. It is used diagnostically to exacerbate mitral valve prolapse for echocardiograms. It can cause brief panic and anxiety. Panic patients rarely experiment with it twice. Isobutyl nitrite (marketed as "rush" or

"locker room") has similar effects, as can nitroglycerine, used to treat angina pectoris. Nitrites have become more familiar because of their potentially lethal interaction with sildenafil and other erection promoting drugs, whose rise to primacy might curtail the abuse of nitrites.

24.2.6. Combined Systemic Disease (Posterolateral Sclerosis, B-12 deficiency)

Combined systemic disease, a vitamin B-12 deficiency syndrome, can present as panic, even as a feeling of a need to escape. It frequently causes anxiety, paresthesias, weakness, hyperreflexia, and numerous "soft" symptoms easily misdiagnosed as anxiety-related or somatoform. In cases with severe pernicious anemia, the patients might hyperventilate and have other anxiety symptoms (110), but mental symptoms can occur without anemia. Documentation of pernicious anemia or low serum B-12 with impaired absorption establishes the diagnosis. Posterolateral spinal tract degeneration occurs progressively, and the primary physical nature of the illness eventually becomes clear. Neurologic damage can be prevented by early diagnosis and treatment. Vitamin B-12 deficiency causes such a diversity of symptoms, we would be strongly tempted to consider it a 'functional' or somatoform disorder, were it not so easy to diagnose with a few blood tests. We do not consider it a psychiatric disorder because we know the cause.

24.2.7. Diagnoses with many somatic symptoms and no known cause

Fibromyalgia is highly comorbid with panic disorder and phobia. It has even more overlap with depression. Degree of anxiety in these patients is the best correlate of decreased physical functioning (111, 112). Chronic fatigue syndrome is highly comorbid with anxiety symptoms, and also with fibromyalgia (113). Irritable bowel syndrome is highly comorbid with anxiety, depressive and neurasthenic disorders, which contribute importantly to its severity and poor outcome (114, 115). Finally, these three conditions are highly comorbid with each other (115). It is also possible that there is basically one disorder here, and that each specialty, including psychiatry, is like one of the blind men describing his own specialty's part of the elephant (Please see addendum). This elephant's current name is 'somatoform disorder' (116).

24.3. Somatoform Disorders

Anxiety disorders are highly comorbid with somatoform disorders (117, 118), even with refinements in the diagnostic criteria that have reduced the overlap of defining symptoms (14). In view of all the physical comorbidities noted above and the psychiatric comorbidities to follow below, anxiety disorders in fact are part and parcel of somatoform disorders. Anxiety rating scales like the popular Hamilton (119) typically can be divided into 'somatic anxiety' and 'psychic anxiety' subscales. It is 'somatic anxiety' that responds best to the benzodiazepines.

The current wise convention is to diagnose anxiety disorders that are present separately from somatoform disorders also present (14). But before we dismiss any set of symptoms as somatoform or 'psychosomatic,' we might do well to remember the example of 'combined systems disease; and read some 25 to 50 year old textbook of psychiatry, which had 'psychodynamic' explanations for so many diseases we now consider purely medical. Two recent ones to fall were nonspecific urethritis and peptic ulcer, now both recognized as microbial illnesses. Not all physical causes are as easy to find as a vitamin B-12 deficiency. One might miss a heavy metal poisoning, radiation sickness, or some disease little known in our part of the world. Nonetheless, 'the psychological tendency to report multiple physical symptoms' can be measured by the Recent Physical Symptoms Questionnaire (RPSQ),and the Comorbid Medical Conditions Questionnaire (CMCQ) (120).

24.3.1. Malingering

Anxiety symptoms are easy to mimic. Some may feign illness in order to be financially and emotionally supported while giving nothing back, but the most usual reason to falsely claim specific anxiety symptoms is of course to be prescribed anxiolytic drugs that are also nonspecific euphoriants.

While clinicians in practice are reluctant to diagnose or even mention malingering, it is actively identified and documented in prisons. Testing at intake with the Psychological Inventory of Criminal Thinking Styles (PICTS), the 'infrequency (INF) scale correlated with degree of malingering after 3-39 months (121). This shows promise, and waits for more rigorous testing.

24.3.2. Drug Seekers

Patients with primary panic disorder and no previous drug abuse are quite unlikely to abuse sedatives. But many polydrug abusers are inclined to include benzodiazepines, especially those with quick onset like diazepam and alprazolam, in their smorgasbord.

Though anxiety patients treated chronically with sedative drugs typically become physically dependent, this dependence is not associated with the severe psychiatric and social problems typical of drug abusers. Their use patterns more closely resemble those of epileptics physically dependent on their anticonvulsants, or even those of insulin-dependent diabetics. Patients with genuine anxiety disorders rarely take more medication than they need to control their symptoms, and in fact are likely to take less than they need for complete relief. The most distinguishing characteristic of sedative abusers is their rapid dose escalation.

Most of the anxiety symptoms primary drug abusers experience result from drug withdrawal. These anxiety states can be extreme. Sedative abusers report more muscle aches and vomiting than anxious patient's experience.

24.4. Treatment

Physicians ideally should give genuine anxiety patients all the sedation they need, and give the abusers none. The problems arise from the patients who have both an established anxiety diagnosis and an inclination to overuse euphoriant drugs.

There is general agreement among researchers, academicians, and countries with socialized medicine that selective serotonin reuptake inhibitors are the treatment of choice for anxiety disorders (122). This near unanimity of opinion has not made its way down to the prescribing clinicians and certainly not to the patients, who overwhelmingly and vociferously express their preference for the benzodiazepines. This preference is reflected in prescribing patterns (123). And even some dissident academicians have noted there is no evidence SSRIs are superior, and that perhaps the whole question should be reconsidered (124).

It is difficult and expensive to complete a study showing one effective treatment is superior to another, especially after the passage of considerable time. Such studies would need to be large and long, and there seems to be no one interested in funding any. The high-potency benzodiazepines have long been available as inexpensive generics. It has been shown that benzodiazepine with antidepressant is effective weeks sooner than antidepressant alone (125). Dose escalation is a very rare problem: less than 1% in adult and geriatric patients (126). When high potency benzodiazepines are prescribed, the day may come when they are to be withdrawn. This can be done by substituting an adequate dose of clonazepam, then reducing it gradually over seven weeks (127, 128).

Some behavioral psychotherapies have shown promise in panic disorder. Most of panic attacks' physical symptoms, and possibly the attacks themselves, result from hyperventilation (129). So panic patients can be helped by being taught to control their breathing (36, 65).

24.4.1. Antidepressant Withdrawal

Abrupt discontinuation of SSRI medications can cause a rebound in the symptoms they had originally relieved (130). Although tricyclic antidepressants are now rarely prescribed, their abrupt withdrawal can cause an abstinence syndrome of insomnia, vivid nightmares, and extreme anxiety (131). SSRI withdrawal can be mitigated by a slow taper along with longer-acting fluoxetine (132).

24.5. Alcoholism

Alcohol reduces anxiety initially, but prolonged use increases anxiety. Anxious patients can experience severe rebound anxiety the day after moderate drinking. Their rebound following immoderate drinking is made worse by alcohol's toxicity. Patients with primary anxiety disorders often learn on their own to avoid alcohol. In many patients who abuse alcohol and have panic attacks, alcohol is the primary problem and the principal cause of panic symptoms. But anxiety disorders also seem to predispose certain persons to alcoholism. Alcohol abstainers with panic or agoraphobic disorders are more likely than others to have alcoholic relatives (133, 134). The best way to determine whether alcoholism or panic is primary is to ask which began first. Often the anxiety is found to have preceded alcohol problems, and may have caused them (134). If panic attacks first occurred during periods of heavy drinking and the patient is still drinking heavily, it is best to first treat the primary alcoholism. Such patients' panic attacks and agoraphobic symptoms usually cease after alcohol withdrawal, and anti-

TABLE 24.1 Physical illnesses causing anxiety symptoms.

Cardiac	Partial complex seizures
Myocardial infarction	Migraine
Angina pectoris	Transient ischemic attacks
Microvascular angina	Cerebrovascular insufficiency
Congestive heart failure	Brain tumor, especially of third ventricle
Paroxysmal atrial tachycardia	Cerebral syphilis
Cardiac dysrhythmia	Encephalitis
Anemia	Postencephalitic disorders
Mitral insufficiency	Multiple sclerosis
Pulmonary	Meniere's disease
Pulmonary emboli	Subclavian steal syndrome
Asthma	Posttraumatic, postconcussive cerebral syndrome
Endocrine	Wilson's disease
Hyperthyroidism	Huntington's disease
Hypoparathyroidism	Parkinson's disease
Hypoglycemia	Combined system disease; posterolateral sclerosis
Pheochromocytoma	Myasthenia gravis
Cushing's disease	Sleep apnea
Diabetes mellitus	Sleep terrors
Pancreatic carcinoma	Sleep paralysis
Hypopituitarism	Dream anxiety attacks
Eosinophilic pituitary adenoma	Drug-induced, intoxications
Thyroiditis	Caffeine, theophylline
Addison's disease	Amphetamine
Infections	Ephedrine, pseudoephedrine, phenylpropanolamine
Malaria	Cocaine
Viral pneumonia	Cannabis
Mononucleosis	LSD, psychotomimetic drugs, hallucinogens
Viral hepatitis	Yohimbine
Rheumatic fever	Beta-carboline
Tuberculosis	Cholecystokinin tetrapeptide
Bacteremia	Khat, Methkhat
Viremia	Tobacco
Chronic fatigue syndrome	Withdrawal states
Collagen Vascular	Alcohol
Systemic lupus erythematosis	Sedative-hypnotic
Rheumatoid arthritis	Tobacco
Polyarteritis nodosa	Beta blocker
Temporal arteritis	Antidepressant
Raynaud's phenomenon	Non-drug Toxicities
Metabolic	Arsenic
Hypocalcemia	Mercury
Hypoglycemia	Lead
Dieting or fasting	Bismuth
Malnutrition	Other heavy metal
Low weight	Carbon disulfide
Chronic vitamin deficiency	Organic solvents
Neurologic	
Grand mal seizure disorder	

panic drugs are not needed (134). If a patient has panic disorder which has clearly preceded alcohol abuse, it might have caused the alcohol abuse.

Prescribing potentially addictive anti-panic drugs to these patients poses an obvious risk, but typically they report no other treatment helps. Patients who have once met criteria for alcohol abuse or dependence are probably more likely than others to become addicted to sedative drugs. On the other hand, unabated panic attacks increase the risk of alcoholic relapse, and panic disorder or agoraphobia can be disabling. Anxiety disorders cannot be dismissed as negligible risks compared to chemical dependency. In fact, a diagnosis of anxiety disorder greatly increases the probability of a drinking relapse (133). Table 24.1 summarizes physical illnesses causing anxiety symptoms.

24.6. Other anxiety syndromes

24.6.1. Hypochondriasis

Briquet (135), rejecting the notion that hysteria was caused by a wandering uterus, also dismissed the diagnosis of hypochondriasis as an artifact of clinicians' unwillingness to diagnose hysteria in any man, "for he has no uterus." Most severe hypochondriacs have a syndrome symptomatically indistinguishable from somatoform disorder. Kendell (136) has pointed out that "No natural point of discontinuity between somatization disorder and other forms of somatic complaint has been demonstrated." Barsky and Klerman do find hypochondriasis and somatization to be distinct, though both have high comorbidity with depressive, anxiety, and other psychiatric disorders (137).

Panic disorder and agoraphobia are associated with hypochondriasis, which is diminished when the panic attacks are treated (138). Hypochondriasis is also likely to be seen during episodes of depression. Hypochondriasis comorbid with panic disorder is typically associated with more distress and more numerous symptoms (139). Hypochondriasis can more usefully be thought of as health anxiety (140) in that these individuals are worried about their health, but not using this worry to exploit others.

24.6.2. Specific Phobias

Specific phobias are the most common of psychiatric disorders (141), and are considered instinctive in children. The objects and situations children fear tend to be things that would have been dangerous to children during the ice age: spiders, snakes, bats, cats great and small, enclosed places (which could have caved in), the dark (night predators) or wide-open spaces (fleet predators). Naive chimpanzees have an instinctive and adaptive "snake phobia." Simple phobic disorders probably represent persistence into adult life of instincts that were once useful to survival. Phobia becomes a disorder when it interferes with an individual's life. Conventional wisdom holds that specific phobic disorders respond not to medication but to behavioral psychotherapy, in which patients progressively accustom themselves to the objects they fear.

Specific phobias are now preferentially treated with SSRIs. Patients with simple phobia might have panic symptoms when they are exposed to the specific thing they fear. Those who have spontaneous panic attacks should be considered to have panic disorder, or agoraphobia with panic attacks.

24.6.3. Social Phobia or Social Anxiety Disorder

Social phobias were originally narrowly defined a fear of a single, specific social situation, like public speaking, performing, visiting, using public showers or rest rooms, or eating in public places. These problems were traditionally treated behaviorally, like simple phobias, by instructing patients to gradually overcome the fear situation by exposing themselves to it. But now SSRI and SNRI antidepressants (142) have been found to relieve social anxiety disorder. Benzodiazepines, beta-blockers, anticonvulsants, d-cycloserine, buspirone and atypical antipsychotics have also been found effective (142–144).

Social anxiety disorder is highly comorbid with the other anxiety disorders, depression, alcoholism and drug abuse (145). Social phobic symptoms are associated with a poorer prognosis in patients with panic disorder and secondary depression (145). Surprisingly, in view of conventional wisdom, social phobias are as likely to be improved by the benzodiazepine alprazolam or the monoamine oxidase inhibitor phenelzine as by cognitive-behavioral therapy (146).

24.6.4. Agoraphobia

Most simply, agoraphobia is a fear of leaving home, particularly alone. Most panic disorder patients have multiple phobias, including agoraphobia. Conventional wisdom (147) holds that clinical agoraphobia results from panic patients' increasing avoidance of places or situations in which their panic attacks would be particularly inconvenient or difficult to control. Agoraphobics most particularly avoid places from which escape would be difficult, like bridges or crowded theatres. When they do go to theatres, they favor seats on the aisle and near the door. Panic attacks in agoraphobic patients are more likely to include fear of losing control, while those not associated with agoraphobia are more likely to include dyspnea and dizziness (148).

Up to half of agoraphobics do not have panic attacks (149). Those with panic attacks are more likely to seek treatment, while those with uncomplicated agoraphobia simply stay home. Uncomplicated agoraphobia could resemble other phobias in being a residual childhood instinct, since leaving home alone was and is dangerous for a child.

Agoraphobia is treated with cognitive behavioral therapy, antidepressants and benzodiazepines. Each can be of benefit combined with one or both of the others (150). Late onset agoraphobia differs from other agoraphobia. It is not significantly associated with panic attacks but rather with severe depression, trait anxiety, and poor visuospatial memory (151). Reluctance to leave the home can be adaptive in the elderly, who are vulnerable to others and to getting lost.

24.6.5. Homophobia

Homophobia is not as yet an official psychiatric diagnosis, as homosexuality once was (8). Both 'diagnoses' are mostly reflections of a particular society's customs, and therefore of its laws. In many parts of the United States and many other countries, homosexuality is still sanctioned criminally, and 'homophobia' administratively. A department head can fire a teacher for homophobia one year, and go to prison for sodomy the next.

Some psychoses are associated with self-derogatory delusions or fears that one is the most horrible sort of person imaginable, and for some, 'homosexual panic' has been the fear or belief that one is homosexual. This might represent a reflection of society's values rather than of anything innate, as we don't see it much anymore: other more current horrors have taken its place.

24.6.6. Posttraumatic Stress Disorder; PTSD

Being a soldier changes a person in many of the same ways as being a doctor. Society tends to value and reward its experienced doctors much more highly than its used soldiers, raped women, abused children. American diagnostic convention emphasizes the anxiety aspects of posttraumatic disorder, while other countries consider changes that occur in mood or even personality. PTSD can also follow non-combat traumata, especially early-life abuse (24), sexual molestation (25), rape (26), being bullied (27) or teased (28). There are increasing numbers of women veterans who have been raped in combat settings (152, 153).

In PTSD, anxiety symptoms are attributed to previous terrible experiences. The specific symptoms are closely related to the trauma, and are made worse by reminders of the trauma. Some PTSD sufferers go to great lengths to avoid crowds or social situations; some camp for months in remote areas, others do farm work and avoid coming into town. These avoidance behaviors suggest agoraphobia. The "flashbacks" in which some of these patients reexperience the original trauma, can have the same symptoms as panic attacks (154). PTSD is highly comorbid with psychiatric and medical conditions, poor health, and a decreased quality of life (155).

A great many drugs have had trials in the treatment of PTSD. This would not be so, if responses to the current ones were satisfactory. The International Consensus Group on Depression and Anxiety considers that the SSRI medications are the first that should be prescribed (156). Benzodiazepines are widely prescribed (157) as are second generation antipsychotics (158). Prazosin (159) is clinically effective at reducing nightmares, and can be used even in soldiers on active duty. The usual hypnotics are used for insomnia.

24.6.7. Obsessive Compulsive Disorder (OCD)

There are still a small number of intractable OCD cases. Comorbidity of obsessive and compulsive symptoms with an episode of major depression is a rare example of a favorable comorbidity. In these patients, symptoms of OCD can remit as the depression does. With or without comorbid depression or panic disorder, symptoms of OCD can easily be treated with higher doses of SSRI antidepressants, or more difficultly with clomipramine (160–163). The most severe cases respond only to psychosurgery, in which parts of the brain are ablated (164). A major review of psychosurgery expresses hope it can be replaced by deep brain stimulation (164), on evidence mostly hoped for.

24.6.8. Hoarding disorder

Bees hoard honey, squirrels hoard nuts, but neither is disorderly about it. Our farmer ancestors' success depended heavily on keeping what they had, but usually their homes were kept neat and tidy. The hoarded food, supplies, implements, fuel and were stored where they would be used. Hoarding as a disorder is mostly detected when clutter impedes the normal use of living spaces (165), which in urban settings are increasingly limited. Hoarding disorder comorbid with obsessive compulsive disorder seems less than might be expected, and more with depression, impulse control disorders (166), and especially inattention (166, 167).

24.6.9. Generalized Anxiety

Generalized anxiety disorder is the most prevalent anxiety disorder in primary care (168). It is so highly comorbid with other psychiatric disorders that uncomplicated cases are difficult to find for therapeutic trials. Its defining symptoms are almost identical to those that respond to benzodiazepines, but antidepressants are also found significantly effective (169). Even so, the condition is highly disabling (169).

24.7. Depressive Disorder

Every anxiety disorder/syndrome strongly increases the risk of depression, and anxiety and depression occurring together respond less well to treatment than either disorder alone, have more severe symptoms, more suicidality, poorer outcome, more disability, and greater social cost (170–175). Comorbid posttraumatic stress disorder has similar adverse effects on depression (176).

24.8. Bipolar Disorder

Anxiety disorders are more associated with bipolar than with unipolar disorder (177). Anxiety disorders (178), especially generalized anxiety and social phobia (179) are associated with poor bipolar disorder outcome.

24.9. Psychoses

Anxiety symptoms are significant in psychotic disorders, 59.8% in the past year in a large study (180). Anxiety diagnoses are present in 38.3% of persons with schizophrenia spectrum disorders (181). Panic attacks during adolescence are a risk factor for psychoticism in young adulthood (182). Psychotic affective disorders are highly comorbid with anxiety disorders (183). The same is true of schizophrenia (184–186).

Schizophrenia is associated with anxiety disorders including social phobia, obsessive compulsive disorder, generalized anxiety disorder, panic disorder, specific phobia, posttraumatic stress disorder and agoraphobia. Even in schizophrenia, anxiety symptoms make the illness worse (186).

So much comorbidity! Can it be the time to have another look at that elephant?

24.10. Addendum

It was six men of Indostan,
To learning much inclined,
Who went to see the Elephant
(Though all of them were blind),
That each by observation
Might satisfy his mind.

The *First* approach'd the Elephant,
And happening to fall
Against his broad and sturdy side,
At once began to bawl:
"God bless me! but the Elephant
Is very like a wall!"

The *Second*, feeling of the tusk,
Cried, -"Ho! what have we here
So very round and smooth and sharp?

To me 'tis mighty clear,
This wonder of an Elephant
Is very like a spear!"

The *Third* approach'd the animal,
And happening to take
The squirming trunk within his hands,
Thus boldly up and spake:
"I see," -quoth he- "the Elephant
Is very like a snake!"

The *Fourth* reached out an eager hand,
And felt about the knee:
"What most this wondrous beast is like
Is mighty plain," -quoth he,-
'"Tis clear enough the Elephant
Is very like a tree!"

The *Fifth*, who chanced to touch the ear,
Said- "E'en the blindest man
Can tell what this resembles most;
Deny the fact who can,
This marvel of an Elephant
Is very like a fan!"

The *Sixth* no sooner had begun
About the beast to grope,
Then, seizing on the swinging tail
That fell within his scope,
"I see," -quoth he,- "the Elephant
Is very like a rope!"

And so these men of Indostan
Disputed loud and long,
Each in his own opinion
Exceeding stiff and strong,
Though each was partly in the right,
And all were in the wrong!

MORAL,

So, oft in theologic wars
The disputants, I ween,
Rail on in utter ignorance
Of what each other mean;
And prate about an Elephant
Not one of them has seen!

-John Godfrey Saxe

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25
Thought Disorder

Nancy C. Andreasen, M.D., Ph.D.

Abstract Thought disorder is an important symptom complex in schizophrenia. This chapter sets out to define thought disorder and the boundaries of thought disorder. Positive and negative symptoms and the speech patterns are described. Finally, the diagnostic significance and the relationship of thought disorder and other symptoms of schizophrenia are discussed.

Keywords Disorganized speech · Negative thought disorder · Positive thought disorder · Schizophrenia · Language

25.1. Introduction

The term thought disorder is confusing to medical students, residents, and senior clinicians alike. The confusion arises because the term thought disorder has no universally agreed definition, although some consensus has begun to emerge during the past 5–10 years. Some clinicians use the term very broadly to refer to such varied phenomena as disorganized speech, confusion, delusions, or even hallucinations. Others restrict the definition to a much narrower concept, sometimes referred to as frontal thought disorder or disorganized speech that is presumed to reflect disorganized thinking.

25.2. Definition

Kraepelin and other great clinicians of the late nineteenth and early twentieth centuries frequently described abnormalities in language and cognition among the patients whom they observed (1). The concept of thought disorder derives principally from Bleuler (2), who defined it in terms of the association psychology that prevailed during his era and believed that it occurred only in schizophrenia:

> Certain symptoms of schizophrenia are present in every case and at every period of illness even though, as with every other disease symptom, they must have attained a certain degree of intensity before they can be recognized with any certainty.... For example, the peculiar association disturbance is always present, but not each and every aspect of it… Besides these specific or permanent symptoms, we can find a host of other, more accessory manifestations such as delusions, hallucinations, or catatonic symptoms… As far as we know, the fundamental symptoms are characteristic of schizophrenia, while the accessory symptoms may also appear in other types of illness…

It is not clear precisely what Bleuler means by "association disturbance," but he appears to be referring to many types of confused thinking, which are usually expressed in confused speech.

Bleuler's ideas have been very influential in modem psychiatry. Until recently, thought disorder was considered to be the pathognomonic symptom of schizophrenia. During past decades, clinicians and psychologists have developed many different methods for assessing this important symptom, including the use of proverb interpretation, IQ testing, perceptual tests such as the Rorschach or thematic apperception test, neuropsychological tests such as the Stroop or continuous performance test, or

N.C. Andreasen, M.D., Ph.D. (✉)
The Andrew H. Woods Chair of Psychiatry, Director, Mental Health Clinical Research Center,
Department of Psychiatry, University of Iowa Carver College of Medicine, Iowa City, IA, USA
e-mail: nancy-andreasen@uiowa.edu

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even the use of physiologic techniques to measure attention, such as eye tracking, single photon emission computed tomography, or positron emission tomography (3–15). Thought disorder is sometimes used as loosely equivalent to cognitive disorder, and cognition is an extremely broad concept.

In a clinical setting, it is probably useful to simplify the concept somewhat. In his classic text on psychopathology, Frank Fish (16) outlined a logical system for categorizing abnormalities in cognition that is quite useful. He suggested dividing them into four main groups: disorders of perception, disorders of content of thought, disorders of process of thought, and disorders of form of thought. At its broadest, thought disorder is sometimes used to refer to all of these. At its narrowest, it refers only to "formal thought disorder" or disorders in process of thought.

Perceptual disorders are abnormalities in perceptual experiences. The most common perceptual abnormalities seen in psychiatric patients are hallucinations of various types. Hearing voices that are not really there, seeing forms that in fact do not exist, or experiencing a sensation of bugs crawling on one's skin when one is not infested are all types of perceptual disorders.

Disorders in content of thought are abnormalities in beliefs and in interpretation of experiences. The most common disorders in content of thought seen in psychiatric patients are delusions of various types. Typical delusions include beliefs such as that messages are being given over the radio or TV about the person, that people are conspiring against the person and trying to harm him or her, or that a person has some type of special or unusual ability.

Disorders in the process of thought involve abnormalities in the way ideas and language are formulated before they are expressed. Unlike hallucinations or delusions, which are usually determined to be present because the patient describes them, thought process disorders are usually inferred by observing what the patient says or does and only occasionally by self-report. One common manifestation of thought process disorder is pressured speech, in which the patient tends to speak loudly, intensely, and rapidly. Another common clinical manifestation is blocking, in which the patient stops suddenly in the middle of a sentence because he or she has lost the train of thought for some reason. Disordered thought processes also may be reflected by impaired attention, poor memory, or difficulty in formulating abstract concepts. These aspects of impaired thinking are assessed through observing the patient or through using simple mental status tests such as serial sevens or memory tests.

Disorders in the form of thought, or formal thought disorders, are abnormalities in the way thought is expressed in language, whether it be in speech or in writing. Clinically, this abnormality appears in various types of disorganized speech which are given a variety of different names (defined in more detail below), such as incoherence, tangentiality, or derailment (loose associations). This type of thought disorder is assessed simply by listening to the patient talk or by looking at his or her writing. The clinician observes the patient's verbal output and determines whether it is well connected, well organized, and seems to make sense or whether, on the other hand, it seems disconnected, disorganized, and bizarre.

The boundaries between these four types of cognitive abnormalities are not always clear. For example, when a patient feels a crawling sensation and then interprets it as due to an infestation of parasites living in his or her bed, is this a delusion, a hallucination, or both? (Probably both.) When a patient speaks very rapidly, skips from topic to topic, makes little sense, and admits that his or her thoughts seem to be occurring too rapidly to control, is this a disorder of thought process or thought form? (Again, probably both.) Further, some patients may clearly display all four classes of cognitive abnormality, while others may display one or two. The four types may, in theory, be mutually exclusive, but they may co-occur as symptoms in actual patients.

Other chapters in this book will focus in more detail on the first two types of cognitive abnormalities, disorders in perception (hallucinations) and disorders in content of thought (delusions). This chapter describes some common clinical manifestations of the last two types of cognitive abnormalities, disorders in the process of thought (dyslogias) and disorders in the form of thought (dysphasias).

25.3. What Are the Boundaries of Thought Disorder?

Don't people who are otherwise normal sometimes speak in a disorganized manner? Doesn't everyone occasionally experience blocking or a rapid flood of ideas? How does one draw the line between "normal thinking" and "thought disorder"?

The following passage from James Joyce's last novel, Finnegan's Wake, illustrates the problem in an extreme case:

> Oh, by the way, yes another thing occurs to me. You let me tell you, with the utmost politeness, where ordinarily designed, your birth wrong was, to fall in with the Plan, as out nationals should, as all nationalists must, and do a certain office (what, I will not tell you) in a certain holy office (nor will I say where) during certain agonizing office hours from such a year to such an hour on such and such a date at so and so much a week (which, May I remind, were just a gulp for you, failing in which you might have taken the scales off boilers like any boskp of Yorek) and do your little two bit and thus earn from the nation true thanks, right here in our place of burden, your boume of travel and ville of tares, (17).

Joyce is using a language in an idiosyncratic and confusing way, relying on punning, wordplay, and allusion. When this sample of speech was given to a group of clinicians to read blindly for severity of thought disorder and to assign a diagnosis, 95 % of the clinicians thought it displayed thought disorder, and 48 % diagnosed its author as having schizophrenia (18).

This result indicates that even clinicians are not clear on the boundaries of abnormal thinking, particularly when they must look at examples out of context and cannot rely on important clinical cues, such as the appearance of the individual, his or her manner of speech, the presence or absence of other symptoms, and past history. The boundaries of thought disorder are particularly blurred when language is used creatively, when it is used pedantically, or when it is used poorly because of low intelligence or inadequate education.

The difference between the creative use of language and thought disorder is largely a matter of intent and control rather than in the nature of the language actually produced. Writers depend on unusual associations to find fresh imagery and then enjoy playing with words and ideas, which may seem to represent "loose associations" or "derailment," however, writers and other creative individuals usually have their cognition under control, and they have a method in their madness. Because of this, an organization usually can be seen in the apparent disorganization, and the result is said to be "creative" or "original". On the other hand, patients who are psychotic are usually out of control, and their language and thinking are therefore perceived as disorganized rather than disciplined and as bizarre rather than creative.

Pedantic use of language also may resemble thought disorder. Verbose, pedantic, empty language is a hazard of some occupations or disciplines, such as politics, administration, philosophy, the ministry, and science. People in these occupations or disciplines may tend to speak verbosely, with excessive use of obscure or overly abstract terminology, and to say very little. Patients suffering from psychosis may have a similar problem, which is referred to as poverty of content of speech. Again, drawing the line between a "normal" thought disorder manifested by a government employee speaking bureaucratese and a psychotic patient with a thought disorder will depend heavily on contextual cues. Is the speaker in control? Can the speaker moderate his or her style if requested to be more specific or more concise? Can the speaker do better on another topic? Does the speaker have any other significant symptoms?

Finally, people who are mentally dull or uneducated also may show some characteristics similar to those patients with relatively severe psychopathology. The mentally handicapped or uneducated may be excessively concrete, may be unable to speak clearly and fluently in reply to a question, may use words idiosyncratically because they do not understand what they mean, or may use poor grammar. Unlike the creative individual or the bureaucrat, these individuals do not have conscious control and cannot shift their language patterns on request. In this instance, clinicians must evaluate their language and thinking in terms of norms adjusted for their intellectual and educational levels. They must take into account information concerning the number of years of schooling, level of performance, and intelligence testing.

Thus, thought disorder is probably not a phenomenon discontinuous from normality but rather is probably on a continuum with it. It may occur occasionally in the speech of normal people, particularly when they are fatigued or disinhibited, and it may occur more frequently in the conscious productions of artists. Whenever the clinician recognizes that he or she is reading or listening to an unusual language and thinking, he or she must always evaluate it in terms of its context. He or she must ask questions such as the following: Is the abnormality under conscious control? Can it be varied and reversed to normal through prompting or through a change of subject? Does the patient have other symptoms? What is the patient's educational and intellectual background? Usually, intelligent use of context will help the clinician distinguish between normal thought disorder and thought disorder that has a pathologic significance.

25.4. What Are the Common Types of Thought Disorder?

Thought disorder is a heterogeneous phenomenon. During the past 50 years, clinicians have described many different manifestations of thought disorder, such as derailment, incoherence, tangentiality, poverty of speech, etc. The many different subtypes also have been a source of confusion, since they tend to be referred to as the global term thought disorder. During recent years, efforts have been made to define the various subtypes more carefully and precisely and to examine the relationship of the various subtypes to clinical diagnosis.

One recent approach has been to subdivide types of thought disorder into two main groups: negative and positive thought disorders. This distinction has been useful because some evidence suggests that negative thought disorders are more common in schizophrenia and also may predict a somewhat poorer prognosis, while positive thought disorders occur in both mania and schizophrenia and may predict a better outcome. Standard definitions of these types of thought disorder are as follows (19).

25.4.1. Negative Thought Disorders

25.4.1.1. Poverty of Speech

This is a restriction in the amount of spontaneous speech so that replies to questions tend to be brief, concrete, and unelaborated. Unprompted additional information is rarely provided. For example, in answer to the question, "How many children do you have?" the patient replies, "Two. A girl and a boy. The girl is thirteen and the boy ten." "Two" is all that is required to answer the

question, and the rest of the reply is additional information. Replies may be monosyllabic, and some questions may be left unanswered altogether. When confronted with this speech pattern, the interviewer may find himself or herself frequently prompting the patient in order to encourage elaboration of replies. Doing an interview to evaluate a patient with poverty of speech can be a very hard work. To elicit this finding, the examiner must allow the patient adequate time to answer and to elaborate the answer.

Example. Interviewer: "Do you think there's a lot of corruption in the government?" Patient: "Yeah, seems to be." Interviewer: "Do you think Oliver North was fairly treated?" Patient: "I don't know." Interviewer: "Were you working at all before you came to the hospital?" Patient: "No." Interviewer: "What kinds of jobs have you had in the past?" Patient: "Oh, some janitor jobs, painting." Interviewer: "What kind of work do you do?" Patient: "I don't." Interviewer: "How far did you go in school?" Patient: "Eleventh grade." Interviewer: "How old are you?" Patient: "Eighteen."

25.4.1.2. Poverty of Content of Speech

Although replies are long enough so that speech is adequate in amount, such replies convey little information in this disorder. Language tends to be vague, often overabstract or overconcrete, repetitive, and stereotyped. The interviewer may recognize this finding by observing that the patient has spoken at some length but has not given adequate information to answer the question. Alternatively, the patient may provide enough information but require many words to do so that a lengthy reply can be summarized in a sentence or two. Sometimes the interviewer may characterize the speech as "empty philosophizing."

Example. Interviewer: "OK. Why, why is it, do you think, that people believe in God?" Patient: "Well, first of all because, he uh he are the person that is their personal savior. He walks with me and talks with me. And uh, the understanding that I have urn, a lot of peoples, they don't really uh know they own personal self. Because, uh, they ain't they all, just don't know they personal self. They don't know that he uh, seems like to me a lot of em don't understand that he walks and talks with them. And uh, show them their way to go. I understand also that every man and every lady is just not pointed in the same direction. Some are pointed different. They go in their different ways. The way that uh Jesus Christ wanted em to go. Me myself I am pointed in the ways of uh knowing right from wrong and doing it. I can't do no more, or no less, than that."

25.4.1.3. Blocking

This is an interruption of a train of speech before a thought or idea has been completed. After a period of silence which may last from a few seconds to minutes, the person indicates that he or she cannot recall what he or she had been saying or meant to say. Blocking should only be judged to be present either if a person voluntarily describes losing his or her thought or if upon questioning by the interviewer, the person indicates that that was his or her reason for pausing.

25.4.1.4. Perseveration

This involves persistent repetition of words, ideas, or subjects so that once a patient begins to refer to a particular subject or use a particular word, he or she continually returns to it in the process of speaking.

Example. Interviewer: "Tell me what you are like, what kind of person you are." Patient: "I'm from Marshalltown, Iowa. That's sixty miles northwest, northeast of Des Moines, Iowa. And I'm married at the present time. I'm thirty-six years old. My wife is thirty-five. She lives in Garwin, Iowa. That's fifteen miles southeast of Marshalltown, Iowa. I'm getting a divorce at the present time. And I am presently in a mental institution in Iowa City, Iowa, which is a hundred miles southeast of Marshalltown, Iowa."

25.4.2. Positive Thought Disorders

25.4.2.1. Derailment (Loose Associations, Flight of Ideas)

This is a pattern of spontaneous speech in which the ideas slip off the track onto another one which is clearly but obliquely related or onto one that is completely unrelated. Things may be said in juxtapositions that lack a meaningful relationship or the patient may shift idiosyncratically from one frame of reference to another. At times there may be a vague connection between the idea, and at others none will be apparent. This pattern of speech is often characterized as sounding "disjointed." Perhaps the most common manifestation of this disorder is a slow, steady slippage, with no single derailment being particularly severe, so that the speaker gets farther and farther off the track with each derailment without showing an awareness that his or her reply no longer has a connection with the question that was asked. This abnormality is often characterized by lack of cohesion between clauses and sentences and by unclear pronoun references.

Although less severe derailments (i.e., those in which the relationship between juxtaposed ideas is oblique) have sometimes been referred to in the past as tangentiality or as flight of ideas when in the context of mania, such distinctions are not recommended because they tend to be unreliable. Flight of ideas is a derailment that occurs rapidly in the context of pressured speech. Tangentiality is defined as a different phenomenon in that it occurs as the immediate response to a question.

Example. Interviewer: "Did you enjoy doing that?" Patient: "Um-hm. Oh hey well I, I oh I really enjoyed some communities I tried it, and the next day when I'd be going out you know, um I took control like uh, I put, um, bleach on my hair in, in California. My roommate was from Chicago, and she was going to the junior college. And we lived in the Y.M.C.A. so she wanted to put it, um, peroxide on my hair, and she did, and I got up and looked at the mirror and tears came to my eyes. Now do you understand it, I was fully aware of what was going on but why couldn't I, why the tears? I can't understand that, can you?" Interviewer: "No." Patient: "Have you experienced anything like it?" Interviewer: "You just must be an emotional person That's all." Patient: "Well, not very much, I mean, what if I were dead? It's funeral age. Well I um? Now I had my toenails, uh, operated on. They're uh, um got infected and I wasn't able to do it but they won't let me at my tools. Well."

25.4.2.2. Incoherence (Word Salad, Jargon Aphasia, and Paragrammatism)

This is a pattern of speech which is essentially incomprehensible at times. The incoherence is due to several different mechanisms, which may sometimes all occur simultaneously. Sometimes, portions of coherent sentences may be observed in the midst of a sentence that is incoherent as a whole. Sometimes, the disturbance appears to be at a semantic level so that words are substituted in a phrase or sentence such that the meaning seems to be distorted or destroyed; the word choice may seem totally random or may appear to have some oblique connection with the context. Sometimes, "cementing words" (coordinating and subordinating conjunctions such as and or although and adjectival pronouns such as the, a, and an) are deleted.

Incoherence is often accompanied by derailment. It differs from derailment in that in incoherence the abnormality occurs within the level of the sentence or clause that contains words or phrases that are joined incoherently. The abnormality in derailment involves unclear or confusing connections between larger units, such as sentences or clauses.

This type of language disorder is relatively rare. When it occurs, it tends to be severe or extreme, and mild forms are quite uncommon. It may sound quite similar to a Wernicke's aphasia or jargon aphasia, and in these cases the disorder should only be called incoherence (thereby implying a psychiatric disorder as opposed to a neurologic disorder) when history and laboratory data exclude the possibility of a known organic etiology and clinical testing for aphasia is negative.

Example. Interviewer: "Why do you think people believe in God?" Patient: "Um, because making a do in life. Isn't none of that stuff about evolution guiding isn't true any more now. It all happened a long time ago. It happened in eons and cons and stuff they wouldn't believe in him. The time that Jesus Christ people believed in their things people believed in, Jehovah God that they didn't believe in Jesus Christ that much."

Interviewer: "Um, what do you think about current political issues like the energy crisis?" Patient: "They're destroying too many cattle and oil just to make soap. If we need soap when you can jump into a pool of water, and then when you go to buy your gasoline, my folks always thought they should, get pop but the best thing to get is motor oil, and, money. May, may as well go there and, trade in some, pop caps and, uh, tires, and tractors to grup, car garage, so they can pull cars away from wrecks, is what I believed in. So I didn't go there to get no more pop when my folks said it. I just went there to get a ice cream cone, and some pop, in cans, or we can go over there and get a cigarette. And it was the largest thing you do to get cigarettes' cause then you could trade off, what you owned, and go for something new, it was sentimental, and that's the only thing I needed was something sentimental, and there wasn't anything else more sentimental than that, except for knickknacks and most knick-knacks, these cost thirty to forty dollars to get, a good billfold, or a little stand to put on your desk."

25.4.2.3. Tangentiality

This involves replying to a question in an oblique, tangential, or even irrelevant manner. The reply may be related to the question in some distant way. Or the reply may be unrelated and seem totally irrelevant. Tangentiality has sometimes been used as roughly equivalent to loose associations or derailment. The concept of tangentiality has been partially redefined so that it refers only to replies to questions and not to transitions in spontaneous speech.

Example. Interviewer: "What city are you from?" Patient: "Well, that's a hard question to answer because my parents … I was born in Iowa, but I know that I'm white instead of black so apparently I came from the North somewhere and I don't know where, you know. I really don't know where my ancestors came from. So I don't know whether I'm Irish or French or Scandinavian or I don't believe I'm Polish but I think I'm I think I might be German or Welsh. I'm not but that's all speculation and that that's one thing that I would like to know and is my ancestors you know where did I originate? But I never took the time to find out the answer to that question."

25.4.2.4. Illogicality

This is a pattern of speech in which conclusions are reached that do not follow logically. This may take the form of non sequiturs (meaning "it does not follow"), in which the patient makes a logical inference between two clauses that are unwarranted or illogical. It may take the form of faulty inductive inferences. It also may take the form of reaching conclusions based on a faulty premise without any actual delusional thinking.

Example. "Parents are the people that raise you. Anything that raises you can be a parent. Parents can be anything, material, vegetable, or mineral, that has taught you something. Parents would be the world of things that are alive, that are there. Rocks, a person can look at a rock and learn something from it, so it could be a parent."

25.4.2.5. Clanging

This is a pattern of speech in which sounds rather than meaningful relationships appear to govern word choice so that the intelligibility of the speech is impaired and redundant words are introduced. In addition to rhyming relationships, this pattern of speech also may include punning associations so that a word similar in sound brings in a new thought.

Example. "I'm not trying to make noise. I'm trying to make sense. If you can make sense out of nonsense, well, have fun. I'm trying to make sense out of sense. I'm not making sense (cents) anymore. I have to make dollars."

25.4.2.6. Neologisms

This involves new word formations. A neologism is defined here as a completely new word or phrase whose derivation cannot be understood. Sometimes, the term neologism also has been used to mean a word that has been incorrectly built up but with origins that are understandable as due to a misuse of the accepted methods of word formation. For purposes of clarity, these should be referred to as word approximations. Neologisms are quite uncommon.

Example. "I got so angry I picked up a dish and threw it at the geshinker." "So I sort of bawked the whole thing up."

25.4.2.7. Pressured Speech

This is an increase in the amount of spontaneous speech as compared with what is considered ordinary or socially customary. The patient talks rapidly and is difficult to interrupt. Some sentences may be left uncompleted because of an eagerness to get on to a new idea. Simple questions that could be answered in only a few words or sentences are answered at great length so that the answer takes minutes rather than seconds and indeed may not stop at all if the speaker is not interrupted. Even when interrupted, the speaker often continues to talk. Speech tends to be loud and emphatic. Sometimes, patients with severe pressure will talk without any social stimulation and even though no one is listening. When patients are receiving phenothiazines or lithium, their speech is often slowed down by the medication, and then it can be judged only on the basis of amount, volume, and social appropriateness. If a quantitative measure is applied to the rate of speech, then a rate greater than 150 words per minute is usually considered rapid or pressured. This disorder may be accompanied by derailment, tangentiality, or incoherence, but it is distinct from them.

25.4.2.8. Distractible Speech

During the course of a discussion or interview, the patient stops talking in the middle of a sentence or idea and changes the subject in response to a nearby stimulus, such as an object on a desk, the interviewer's clothing or appearance, etc.

Example. "Then I left San Francisco and moved to … Where did you get that tie? It looks like it's left over from the 50s. I like the warm weather in San Diego. Is that a conch shell on your desk? Have you ever gone scuba diving?"

25.5. Diagnostic and Prognostic Significance of Thought Disorder

Bleuler, the psychiatrist responsible for introducing the term schizophrenia, believed that thought disorder occurred only in schizophrenia. However, Bleuler's beliefs about the specificity of thought disorder have been questioned. A number of investigators have observed that thought disorder may occur in other diagnostic groups, such as manic patients, and that abnormalities in speech and thinking also occur in normal people. Finally, it has been observed that not all schizophrenic patients display thought disorder, thereby raising additional questions about its diagnostic specificity.

TABLE 25.1. Frequency of types of thought disorder in psychiatric patients.

	Manic patients ($N=32$)		Depressives ($N=36$)		Schizophrenics ($N=45$)	
	N	Percent	*N*	Percent	*N*	Percent
Negative thought disorder						
Poverty of speech	2	6	8	22	13	29
Poverty of content of speech	6	19	6	17	18	40
Blocking	1	3	2	6	2	4
Perseveration	11	34	2	6	11	24
Positive thought disorder						
Derailment	18	56	5	14	25	56
Incoherence	5	16	0	0	7	16
Tangentiality	11	34	9	25	16	36
Illogicality	8	25	0	0	12	27
Clanging	3	9	0	0	0	0
Neologisms	1	3	0	0	1	2
Pressured speech	23	72	2	6	12	27
Distractible speech	10	31	0	0	1	2

After the preceding definitions were developed, they were applied to consecutive admissions to the Iowa Psychiatric Hospital (20, 21). The frequency with which various types of thought disorder could be found in various diagnostic groups was then determined. The results are shown in Table 25.1.

As Table 25.1 indicates, manic patients have a great deal of formal thought disorder. Pressured speech, as might be expected, is their most prominent symptom, but they also have high rates of derailment, tangentiality, incoherence, and loss of goal. Incoherence does not occur with great frequency, but the frequency is equal to that found in schizophrenia. On the other hand, schizophrenic patients tend to have relatively more negative thought disorder than do the manic patients, but they also have relatively high rates of some types of positive thought disorder. The depressive patients have very little thought disorder. Their most prominent types are poverty of speech, poverty of content of speech, and circumstantiality.

These data have been replicated in several subsequent investigations (22). They confirm the fact that thought disorder is not pathognomonic of any particular type of psychosis. When thought disorder is divided into subtypes, such as positive versus negative, it may have somewhat more diagnostic significance. In particular, negative thought disorder in the absence of a full affective syndrome is highly suggestive of schizophrenia. These results also indicate the utility of subdividing thought disorder into various clinical subtypes.

Follow-up studies also have been conducted in order to determine the prognostic significance of thought disorder (22). When manic patients are evaluated 6 months after their index evaluation, most clinical manifestations of thought disorder (such as derailment or pressured speech) have fallen to normal levels. Thus, manic thought disorder, while transiently as severe as that occurring in schizophrenia, tends to be reversible.

On the other hand, the thought disorder observed in schizophrenic patients is somewhat more complex. The negative thought disorders continue to persist for 6 months later and even to worsen. On the other hand, the positive thought disorders tend to diminish somewhat. When types of thought disorder are correlated with other measures of outcome, such as ability to work or to relate in normal social settings, then negative thought disorder is found to be a powerful predictor of outcome. Patients who had prominent negative thought disorder at index evaluation tended to perform poorly on measured social functioning 6 months later. Thus, thought disorder, and particularly the type of thought disorder, has considerable clinical and prognostic significance.

25.6. Relationship Between Thought Disorders and Other Symptoms of Schizophrenia

Although we now recognize that various types of thought disorder may occur frequently in mood disorders as well as schizophrenia, the concept of thought disorder still remains quite central to the definition of schizophrenia. Because the symptoms of schizophrenia are varied and complex, during the past decades clinicians have developed a system for simplifying and clarifying them by dividing them into two general groups: positive and negative. In general, positive symptoms are defined as a distortion or exaggeration of normal functions; conventionally, they include hallucinations (a disorder of perception), delusions (a disorder of inference), bizarre or disorganized behavior (a disorder of behavioral organization and control), positive

formal thought disorder (disorganization of speech), and possibly inappropriate affect; negative symptoms represent a loss or diminution of function and include alogia (negative thought disorder such as poverty of speech), affective blunting, anhedonia and asociality, avolition, and possibly attentional impairment (23–27).

A large literature suggests that these two constellations of symptoms may identify important correlates of schizophrenia that have predictive value. Crow (28) was the first to suggest that a syndrome characterized by negative symptoms typically manifests an early age of onset, poor premorbid adjustment, poor response to treatment with neuroleptics, indices of cognitive dysfunction ascertained with neuropsychological assessment, and evidence of structural brain abnormalities assessed with neuroimaging; the positive syndrome, on the other hand, may be characterized by better premorbid adjustment, later age of onset, good response to treatment, intact cognition, and absence of structural brain abnormalities. Crow hypothesized that the negative syndrome might represent a more "structural" and therefore irreversible form of schizophrenia, while the positive syndrome would represent a more neurochemical and reversible form.

Since Crow's original formulation, this distinction has been repeatedly evaluated in large numbers of research investigations. A consensus currently exists that the distinction between positive and negative symptoms is globally useful and that these symptoms are often correlated with other clinical features as originally described by Crow, although the relationship is by no means sufficiently strong to identify distinct subtypes of schizophrenia or to have consistent predictive validity. That is, prominent negative symptoms do typically suggest a worse outcome, but any individual patient with prominent negative symptoms may do well, respond to medication, and have normal indices of brain function. The same type of generalization can be made concerning the predictive validity of positive symptoms. Because this distinction has heuristic value, the definition of schizophrenia in DSM-IV will incorporate the concept of positive versus negative symptoms. Although an oversimplification, the distinction between positive and negative symptoms is a clinically useful oversimplification.

One of the criticisms that have been launched against the distinction is that a simple subdivision of the symptoms of schizophrenia into positive and negative does not completely account for the complexity of thought disorder and its relationship to other positive symptoms. As described above, thought disorder is both positive and negative, with negative thought disorder encompassed in the concept of alogia and positive thought disorder encompassed in forms that manifest as very disorganized speech such as derailment and incoherence. Further, several studies have examined the relationship between positive thought disorder and other positive symptoms and have consistently demonstrated, using factor analysis, that two symptom clusters tend to occur within the group of positive symptoms (29–31). While negative symptoms tend to be highly correlated with one another, positive symptoms subdivide themselves into two separate groups. One group tends to have high factor loading on positive thought disorder and bizarre behavior; this group probably represents a "disorganization factor." In addition, inappropriate affect also tends to cluster with these two symptoms. The other major factor, with high loadings on delusions or hallucinations, may be considered a psychoticism factor.

A consensus is emerging that the symptoms of schizophrenia might be best simplified through a division into three broad groups rather than two. One group consists of negative symptoms, while the remaining two dimensions are psychoticism and disorganization. These three dimensions of schizophrenia may represent a more useful conceptualization of its subtypes as well, although considerable work must still be done in order to evaluate this possibility.

25.7. Editor's Comment (From 1994 Edition)

An alternative to the positive/negative distinction in schizophrenia is provided by the extremely complex clinical system of Leonhard (32). Departing from Kraepelin's separation of schizophrenia, Leonhard presents 16 subtypes. There are 6 subtypes of catatonic schizophrenia, 4 subtypes of hebephrenic schizophrenia, and 6 subtypes of paranoid schizophrenia. Leonhard describes the number and quality of symptoms. For an end-state diagnosis of schizophrenia, an individual must fit into a specific combination. As an example of the difference, in parakinetic catatonia, a jerky choreiform set of involuntary movements appears, whereas in manneristic catatonia, posture and movement become stiff. Each of the subgroups is thought to be due to abnormalities in different neurologic systems. It would be very useful to investigate the varieties of thought disorder in the subtypes of schizophrenia that Leonhard presents. As it is, however, both the positive/negative distinction and the Leonhard classification are useful concepts in teaching about psychiatric patients.

25.8. Editor's Comment (From 2016 Edition)

For greater discussion of the various alternatives to positive/negative dichotomy and Leonhard's classification, please see the chapter on schizophrenia and the recent paper by Arnedo et al. (33).

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26
From Phenomenology to Strong Biologism and Epigenetics in Psychiatry

Steven Thurber, Ph.D., ABPP and William Sheehan, M.D.

Abstract An inchoate yet sanguine picture is emerging for a more brain-related epiphenomenal foundation for the understanding and treatment of psychiatric disorders. We review germane advances and impediments in this regard. Encouraging findings in tracking certain anomalous genetic conditions from their origins to effects on neurological structures and functions (strong biologism) are discussed; findings from neuroimaging research are likewise noteworthy, but the search continues for delineation of pathological biomarkers from neuroimaging data. The nature of genetic mediation of adverse environmental effects on the brain and behavior are beginning to be understood in relation to the expanding area of epigenetics. We opine that an extant synthesis of neurobiological and epigenetic information warrants serious and increasing dialogue regarding biologically based diagnoses, treatments, and preventive strategies.

Keywords Strong biologism · Psychiatric diagnoses · Environmental and genetic determinants · Epigenetics

26.1. Introduction

Three earlier editions in *The Medical Basis of Psychiatry* were entitled *Phenomenology of Coarse Brain Disease*. In the most recent chapter, we reported on forces within (cerebral vascular accidents) and outside the brain (e.g., blunt force and pressure injuries) that result in destruction of tissue. In such cases, we confronted findings that the impact of damage was related to the nature of the premorbid brain. What was the degree of brain integrity at the time of hemorrhage or injury in combat, for example. It was not simply the amount of tissue ablated or rendered dysfunctional that directly correlated with extent of the negative sequelae. Brain-injured persons have degrees of resilience and cognitive reserve that result in individual variations in this regard. Subsequently, we have pondered the biological and environmental influences on the brain that can provide resilience as well as factors that are deleterious but more subtle and protracted than the traumatic events discussed in the prior chapters.

The underlying concept in this chapter is that of "material epiphenomenalism," that the medical basis for psychiatry resides in knowledge as to how the brain works in relation to psychiatric disorders. This knowledge is multifaceted, and it pertains to human genome, environmental influences (beginning in the intrauterine environment), and the intersection of genetic-environment effects, the epigenome. We will argue that progress in understanding these determinants of neuropathology will require a more biologically based taxonomy. We will also aver that an adverse early environment (e.g., sexual abuse victimization) can have deleterious effect on the brain equivalent to that of traumatic injuries.

The first two editions on coarse brain disease in the *Medical Basis of Psychiatry* series contained established information on brain localization and certain mental and emotional functions subserved. These chapters then logically involved the examination of anomalous behaviors that emerge when the neurological underpinnings are disturbed. In the third edition, we focused on extreme

S. Thurber, Ph.D., ABPP (✉)
Child and Adolescent Behavior Health Services, Minnesota Department of Human Services,
1701 Technology Drive NE, Willmar, MN 56201-2275, USA
e-mail: steven_thurber@yahoo.com

W. Sheehan, M.D.
Psychiatrist, Child and Adolescent Behavior Health Services, Willmar, MN, USA
e-mail: Sheehan41@charter.net

S.H. Fatemi and P.J. Clayton (eds.), *The Medical Basis of Psychiatry*, DOI 10.1007/978-1-4939-2528-5_26

events—physical brain insults, cerebral vascular accidents—and their adverse sequelae. In the current edition of this chapter, we will extend the nature of "brain insults" to include the impact of negative interpersonal experiences on neurodevelopment.

Earlier, we also questioned the "organic-functional dichotomy" as an inaccurate reflection of brain-behavior relationships together with the diagnostic systems that perpetuate such a distinction. For example, we lamented an imprecise DSM functional "personality disorder" diagnosis assigned to a patient who, clearly according to neuroimaging, had an almost complete ablation of the temporal lobe, a finding that would constitute a specific etiological account for the presenting behavioral symptoms (1). We implied that this type of diagnostic and treatment problem is an inherent weakness in nosological formulations currently used by psychiatrists and other mental health professionals.

In this chapter, we will review progress or lack of the same in advancing etiological diagnoses based on neuropathology and biological considerations. We suggest that a more complete understanding of coarse brain disease will require major modifications in current psychiatric taxonomies. In this regard, we will also supplement the earlier chapters by examining research on genetic determinants of coarse brain diseases. In addition, we will include a section on how environmental factors influence DNA expression in the brain through epigenetic interactions.

26.2. Need for a Biologically Based Taxonomy

Critical concerns about systems for psychiatric classification (e.g., ICD-10, DSM-IV and DSM-5) are rampant. The categorical nature of disorders, diagnostic overlap, low interjudge reliabilities, the absence of laboratory validation, and clinical heterogeneity are just some of the problems that have been delineated. Dean (2) laments the diagnostic overlap among DSM classifications and the fact that this belies the specificity assumptions inherent in the taxonomy together with the assumption of the specific mechanisms of medication effects. Thurber, Sheehan, and Roberts (3) and Achenbach (4) have commented on the "top-down" approach extant in psychiatric nosology. That is, instead of starting at the "bottom" with actual data from reliable behavioral assessments, personality test results, neurological data, and findings from neuroimaging and then proceeding inductively to an appellation that accurately reflects the nature of the data, formulators create committees starting at the "top" with denotatively inexact terms that are debated and negotiated until some form of consensus is achieved. The thoughts of the committee members may have varying degrees of empiricism and likely reflect disparities in theoretical interpretations. It is often only after the committee adjourns that scientific methods are applied to ascertain the credibility of the negotiated consensus. It is difficult at best to develop a reasonable psychiatric taxonomy with the inherent difficulties in delineating but not conflating classifications and the absence of consensually validated theoretical guidance.

The recently published fifth edition of DSM has not assuaged these concerns. If anything, the concerns have been renewed and aggravated. This is especially veridical in relation to the absence in the latest DSM version of demonstrable biological pathways for most of the diagnostic classifications (5). Indeed, the one area of possible consensus among psychiatrists and mental health professionals is *material epiphenomenalism*, the view that pathological mental events have their basis in the structures (from the molecular to the neuronal to neurocircuits) that comprise the human brain, the biochemically mediated interactions between and among these structures and neurosystems, and the resulting functional utility. Ultimately, psychiatric disorders reside in brain systems (6).

26.3. Barriers to Establishing a Neuropathological Nosology

1. *Weak biologism*. Most of what we generally know about biological determinants of behavior is based on the notion of heritable traits. The term "heritability (h^2)" refers to the percentage of a trait associated with genetic transmission. The formulation "$h^2 \neq 0$" (7) seems axiomatic: Of course, heritability will never equal zero. All human characteristics are related to or influenced by genetics; everything about the human being, including the phenotype, is heritable. Heritability is a general term; it does not explain anything about the nature of genetic transmission nor does it explicate how the genes influence brain development and ultimately behavior. Heritability is a concept consistent with what Turkheimer (7) calls "weak biologism". It is similar to Meehl's (1) previously mentioned concept of nonspecific genetic etiology. Heritability is a statistical statement about the percentage of variability of a characteristic (phenotype) determined by the genes; it explains virtually nothing about the nature of the transmission: What is the path from the genes to protein synthesis and eventually to brain development or in the case of adverse mutations, abnormal neuro-structures and functions. A further exemplar of denotative inexplicitness is seen in what behavioral geneticists term the principle of "emergenesis," referring to a genotype being caused by some interactive combination of genes, each one of which remains unidentified. In order to have material epiphenomenal nosology, a strong biologism must be established.
2. *Complexity of genetic transmission*. It is acknowledged that mental and emotional disorders, albeit heritable, do not involve simple (single gene) Mendelian genetic transmission. Rather, a reliable diagnosis may involve numerous genes each with a

relatively small contribution, leading to multifarious genetic (as well as environmental) interactions to produce a complicated diagnostic phenotype. It may be that in the present state of genetic research in psychiatry, a strong biologism is precluded. Instead, the concept of "endophenotype" has been adopted that may facilitate the identification of so-called "susceptibility" genes. Psychiatric diagnoses are multifactorial in nature. A single component of a syndrome (e.g., disordered working memory) can be extracted from the diagnostic classification that becomes the emphasis of study; a major part of the investigation concerns brain structures and functions and neurocircuitry. Once the latter are delineated, a potential endophenotype is posited; then, a search commences for genetic transmission (susceptibility genes) related to neurogenesis.

3. *The difficult search for endophenotypes*. The endophenotype lies between the genes and the behavioral expression of a disorder. It is a mediating variable that for our purposes relates to the neural systems involved in the syndrome. A syndrome is multifaceted and related to the concept of emergenesis, with numerous small effects of specific genes interacting in complicated ways to produce the neurological manifestations. The assignment of an endophenotype begins by decomposing the syndrome and selecting one of its facets as a focal point. This amounts to a type of reduction to a simpler diagnostic structure with a known or potentially discoverable neurocircuit. The next part of the quest is the investigation of the genetic aspect of the simpler diagnostic component. Again, the task of establishing a neurological nosology appears daunting.
4. *Neuroimaging and psychiatric diagnoses*. Thus, there appears to be emerging optimism regarding a solution to some of the diagnostic problems in psychiatry through the burgeoning domain of neuroimaging research. To evaluate this possibility, a special task force of the American Psychiatric Association was recently formed to evaluate whether or not neuroimaging markers for major psychiatric disorders were feasible (8). Unfortunately, this domain is already limited by the DSM classifications and their lack of discriminant validity and clinical heterogeneity (among other difficulties). Nevertheless, there appears to be some sanguinity with respect to the schizophrenic spectrum and fairly consistent neuroimaging findings; PET and SPECT findings that converge in support of the aforementioned dopamine hypothesis (9). There are also consistent findings regarding diffusion tensor imaging and white matter alterations in autism spectrum disorder. However, the task force concluded that on the whole, neuroimaging studies have serious weaknesses in relation to such methodological issues as small sample sizes, low power, lack of replication, and low sensitivity and specificity and inconsistent findings throughout a rather extensive literature. The task force members recommended (obviously) better research methodologies together with increased use of meta-analyses. The committee members concluded that, to date, there are no brain imaging biomarkers that are clinically useful.

26.4. Toward a Stronger Biologism

1. *Fragile X*. This represents the prototype for a neuroscience based on a strong biologism, the capability of neuroscientists in tracing brain development from biological catalysts to actual brain morphogenesis. The nature of the mutation involves the long arm of the X chromosome involving the "silencing" of the FMR1 gene (10). This results in a reduction of the protein product, termed "FMRP." This reduction in turn affects the regulation of brain proteins important in neurodevelopment. Specifically, FMRP appears to affect dendritic spine and synapse maturation as well as pruning. Thus, the brains of individuals with fragile X evince longer, thinner dendrites and increased spine density. The result is anomalous structural and functional epigenesis, all correlated with the protein end product of the FMR1 gene: enlarged caudate nucleus, decreased size of the cerebellar vermis, smaller amygdala, and enlarged fusiform gyrus.

   Increased caudate nucleus volume concatenates with the intellectual deficiencies observed in the fragile X syndrome; decreased size of the cerebellar vermis conflates with deficits in language development, visual-spatial processing, and executive functions seen in the fragile X syndrome. Amygdala and fusiform gyrus dysfunctions relate to the so-called social brain and are associated with difficulties in facial recognition and emotional regulation (11).
2. *Psychosis*. Perhaps the most monumental study to date (certainly the largest) on the human genome and psychiatric disorders was recently completed by the cross-disorder group of the psychiatric genomics consortium (12). The participants included over 30,000 individuals with psychiatric diagnoses (bipolar, schizophrenia, attention-deficit hyperactivity disorder, autism spectrum, and major depression) with over 27,000 control participants. Analyses focused on single nucleotide polymorphisms. Calcium channel signaling genes were implicated across all five disorders. The biological pathways mediated by the CACNA1C (calcium channel, voltage-dependent, L-type, alpha 1c subunit) gene emerged as significant suggesting that dysfunctions in voltage-gated calcium signaling were common across all disorders. The implications relate to genetic determinants that are important in neurocircuitry involved in emotion processing as well as several executive functions common to the disorders surveyed. Intracellular concentration of calcium ions in neurons also relates to regulation of neuron excitability and strength of synaptic concatenations. It makes good sense that calcium channel signaling would emerge as a critical component in general psychiatric dysfunctions (13). Below are findings related to the epigenome and the CACNA1C gene.
3. *Single cell sequencing and genetic mosaicism*. Single-cell sequencing applied to brain cells has produced data proclaimed by the director of the National Institute of Mental Health, Thomas Insel, as one of the top ten discoveries of the year 2013. The findings reported by McConnell et al. (14) relate to neuron-to-neuron genomic differences, termed "genetic mosaic."

Single-cell sequencing profiles the genomes of single neurons in contrast to the prototypical approaches that report global aspects of the genome that may mask such individual differences. The different DNA content of neurons may in turn result in phenotypic differences. Moreover, genetic variability of neurons may eventually yield a deeper understanding of the genetic complexity of disorders such as schizophrenia.

4. *Genetic activating patterns*. Neuroscientists, anatomists, and molecular biologists at the Allen Institute for Brain Science in Seattle have been conducting unprecedented postmortem studies that connect the human genome (i.e., virtually all protein-coding genes) to 900 sampled areas of the human brain. They are able to select a given gene and evaluate its degree of RNA in the various cerebral areas. Among other important findings, there is greater support for neurocircuitry than for specific localization patterns. And, this is the very essence of a strong biologism endeavor. Moreover, the Allen Institute has made their database on gene activity and the brain freely available to psychiatric researchers (15).
5. *Endophenotypes and neuroimaging*. Several endophenotypes have been hypothesized for a variety of disorders. For example, we (16) posited working memory as an endophenotype of ADHD. The known structures and functions of the left inferior frontal gyrus and the dorsolateral and ventrolateral regions of the prefrontal cortex are important in working memory, together with a loop that includes the prefrontal cortex and the basal ganglia, with the functions of the globus pallidus (removes irrelevant information) being a cardinal structure. Working memory has a substantial heritability. The next step in establishing working memory as an endophenotype would be to ascertain the presumed polygenic interactions that affect neurogenesis of relevant brain architecture.

Glahn, Thompson, and Blangero (17) are more sanguine about the feasibility of establishing endophenotypes for psychiatric classifications based on neuroimaging data. They viewed this as necessary in order to move nosology from the phenomenological to the rigor of neuroscience. The authors opined that an actual quantification of brain structures and functions provided by neuroimaging would render genetic influences more easily discoverable.

Their review of reported percentages of variability of brain volumes from neuroimaging research (e.g., intracranial, corpus callosum, gray matter) accounted for by genetic factors was followed by findings related to volume anomalies reliably reported in psychiatric disorders. Moreover, brain volumes (frontal gray matter) are also related to measures of cognitive performance, including IQ. Affective disorders are associated with atrophy in the limbic system; schizophrenia concatenates with more global volumetric attenuation. Furthermore, despite the conclusions of the APA concerning neuroimaging-based psychiatric diagnoses, functional neuroimaging results are sensitive to polymorphisms in genes related to neurotransmitter dysfunctions. It is noteworthy that data from functional neuroimaging may actually be more attuned to genetic variations than maladaptive behavior itself (18, 19).

There is a gene database that provides periodic meta-analyses of the multiple interacting genes that appear pathogenic in schizophrenia. Although ostensibly polygenic and emergenic, a particular gene variant that affects the vesicular monoamine transporter protein that in turn influences dopamine accumulation may be the most important in the pathophysiology of the disorder. Hence, it may be an important endophenotype. Dystrobrevin-binding protein 1, encoded by the DTNBP1 gene, affects neurodevelopment in the axon bundles, cerebellum, and hippocampus. The so-called dopamine hypothesis posits that presynaptic dopamine elevation in the striatum may then cause innocuous external stimuli to have inordinately high-level significance (perceptual abnormalities) and subsequently affect association areas (striatum-prefrontal circuitry) and hence produce commensurate thought dysfunctions (9).

26.5. Conclusions About Modifying Psychiatric Diagnostic Classifications

We submit that there is sufficient foundation for a serious dialogue on the development of a biologically based psychiatric nosology. Such a dialogue might begin with voltage-gated calcium signaling as a potentially common element among several psychiatric symptom clusters while proceeding to factors that are more biologically distinctive. Moreover, the availability of a human genome database (20) along with the advent of genome scanning strategies yields future hope for finding gene interactions that produce distinctive quantified volume deficits, neurotransmitter anomalies, and other neurodevelopmental dysfunctions in psychiatric disorders.

26.6. Environmental Determinants and the Epigenome

Having reviewed some salient data concerning genetic influences on brain structures and functions, we turn now to a discussion of environmental influences on the brain more subtle and enigmatic than the extreme environmental events (i.e., traumatic brain injuries) covered in the previous edition of this chapter. It should also be mentioned that the concept of weak biologism may

have a parallel in the field of environmental influences. Simply to aver that the environment can cause anomalous brain development tells us nothing about specific components of the environment and how those aspects specifically affect the third largest and arguably the most important organ of the human body. Nevertheless, exciting progress is being made in this domain and will be reviewed in this section.

26.6.1. Infrahuman Research

Darwin was among the first scientists to suggest (in *Origins of the Species*) that mental activity per se may affect neurodevelopment. Such an inference emanated from his observed findings of a differential in skull size between domesticated and wild rabbits, that is, reduced environmental complexity in the domesticated setting may have resulted in brain atrophy. Darwin also emphasized the continuity between so-called lower and higher forms of animal life. He marveled at the similarities between apes and humans, that hominins have essentially the same physical architecture as other mammals—homologous bones, nerves, blood vessels, and, importantly, the brain. At the cellular and molecular level, even the brains of rodents and humans are highly congruous (21, 22).

26.6.2. Neuroplasticity of the Rodent Brain

The classic scientific investigations in the 20th century dealing with infrahuman organisms were conducted in the 1960s and 1970s by Rosenzweig and colleagues at the University of California, Berkeley. They demonstrated that the anatomy and neurochemistry of the brain can be altered by differential experiences. The investigators worked with rats from the same genetic strain in comparing possible brain alterations from enriched, standard, and stimulus-deficient laboratory environments. In comparison to impoverished rats, animals placed in the complex environment (several rats per large cage, activity wheels, toys, tunnels, obstacles, environmental challenges, and a variety of stimulus objects) showed thickening of gray matter in the hippocampus, greater neurotransmitter activity, increased blood supply in the brain, greater cortical growth (based on postmortem cell counts), and gliogenesis. Findings were also consistent across studies over time, indicating environmental enhancement in relation to dendritic branching, spine density, synaptogenesis, and angiogenesis (23, 24). Subsequent studies over the next decades with lower mammals have corroborated the plasticity of the brain in responsiveness to environmental stimulation and extended the findings to include neurogenesis and the migration and integration of new neurons even in mature organisms (25). Such changes appear to occur mainly in the hippocampus (26).

Conversely, the ostensive deleterious neurological effects of long-term exposure to adverse and impoverished environments (e.g., reduced cortical development, lowered levels of enzyme activity, decreased neurogenesis) also continue to be documented (27, 28). We will not belabor the point. The question is really related to the extent of cross-species generalization; especially the types of environmental experiences that may antedate psychiatric dysfunctions in humans.

26.6.3. From Rodents to Hominins

It is tempting to generalize blithely from rigorous, well-controlled studies with lower mammals to humans, especially given the Darwinian assumptions related to continuities across subspecies. The lower animal research has involved true experiments with rigorous controls that are ethically unfeasible with humans. Analogous studies with humans are quasi-experimental and correlational in nature. Nevertheless, there are some intriguing parallels in the literature that suggest concatenations in general findings across mammalian species. There are a few studies with humans that show the same type of neuroplasticity in humans found in rodent investigations. For instance, the first report of neurogenesis in the adult human hippocampus was in 1998, inspired by infrahuman research; at the time, this was unexpected, astonishing, and contrary to the extant models of fixed and declining numbers of neurons in the adult brain (29, 30).

The seminal work of Bruce McEwen and colleagues at Rockefeller University is illustrative of adverse environmental effects on the brain that can be extrapolated to humans. In a plethora of studies, the researchers report the impact of environmental stressors causing an imbalance in neural circuitry involving the amygdala, hippocampus, and prefrontal areas of the brain. By far, more is known about the effects of environmental stress factors and deleterious brain development than any other single variable.

Their work has taken them from rodents to humans. More specifically, animal research has involved the notion of "toxic stress" meaning stressors that result in a prolonged activation of the body's stress or mobilization response. High, sustained levels of cortisol or corticotropin-releasing hormone can result in damage to the hippocampus, affecting learning, memory, and the ability to regulate reactions to stress. Children who are neglected or abused, for example, or residing in homes with strong

financial pressures or who are cared for by an adult with severe emotional problems can have elevated cortisol levels or abnormal cortisol release patterns that alter the same brain circuits observed in lower organisms (31). Such cortisol effects early in the lives of children may result in lowered abilities for controlling stress reactions and render them vulnerable to later emotional problems (e.g., depression) and stress-related physical problems (e.g., cardiovascular disorders) (32).

26.6.4. Mechanism of Environmental Impact: Stress and Gene-Environmental Interactions

One way a stressful environment can affect neurodevelopment is through the modification of gene expressions that can affect the development of brain architecture (33). For a cogent review of the topic of experiences altering gene expression, see publications by the Center on the Developing Child, Harvard University (34). In simplified form, stress can affect chemical compounds that can dictate time elements regarding switching particular genes (among the 23,000 that comprise the human genome) on and off. Such chemical instructions at early, sensitive periods of development can play critical and enduring roles in brain architecture and functions; more about these chemical control mechanisms or the "epigenome" will be discussed later.

Another way of looking at environmental and genetic effects for brain psychopathology is obviously that they are not orthogonal but rather interact to produce neurological structures and functions. This is the "gene-environment" perspective, symbolized as GxE. It means that variations in genes moderate environmental risks to the development of psychopathology, a major risk being that of early stressful events or the reverse; genetic vulnerability (predispositions for pathology) is moderated by the nature of environmental events (35).

26.6.5. Epigenetics: Part of the GxE Formulation

As important as genetic determinants may be in facilitating an understanding of neuropathology, there are current investigators who would aver that data concerning the *epigenome* are even more imperative. First, the epigenome is the "intersection" where forces in the individual's environment can affect the genome and hence DNA expressions and protein synthesis in the brain. This is different than the more immediate, palpable traumatic, and vascular insults to the brain, but environmental-epigenetic interactions can be just as insidious. However, secondly, at least some adverse epigenetic mutations (called epi-mutations) are reversible. Third, it is also possible, albeit yet to be demonstrated, that certain forms of psychotherapy may have a salubrious impact on the epigenome and hence affect the genome. Data are already extant that dietary and medication interventions can have such an effect (see below).

Two metaphors have been used to explicate the nature of the epigenome. Randy Jirtle (36), an esteemed pioneer in epigenetic research, views the genome as the "hardware" and the epigenome as the "software." The hardware of the computer is nonfunctional until directed by software programs. Similarly, DNA is dormant without epigenomic regulation. Graff, Kim, Dobbin, and Tsai (37) employ a "book" analogy. The pages represent chromatin (the DNA and proteins comprising the cell nucleus) that must be opened by the epigenome in order for the words (genes) to be read and interpreted, and the information applied.

The well-publicized effect of the environment (i.e., temperature) on gene expression in the alligator (determination of gender) is an obvious case in point. The fact that identical twins evince different phenotypes involves the essence of epigenome regulation. Another graphic example relates to the fact that a genetic predisposition for myopia will not be actuated unless reading and other close visual work interact with the genetic propensity in producing an elongation of the eyeball. These are exemplars of gene expression being modified by the environment.

Champagne and Mashoodh (38) provided a good conceptual explanation on the experience-dependent changes in gene functions related to what is termed "epigenetics" (literally, "epi" means "in addition to" genetic influences, with addition meaning environmental influences). A gene, of course, is a particular sequence of DNA that carries information related to protein synthesis. The sequence is "read" by an enzyme called RNA polymerase, followed by a production of messenger RNA. The messenger RNA is a copy of the gene (DNA sequence) that can lead to the protein synthesis. The possible expressions of the DNA are almost infinite, but the expressions will not be actuated without "additional" processes occurring within a cell. Those processes that lead to an expression of DNA without altering the particular DNA sequence are collectively referred to as "epigenetic."

The main chemical process that can occur "in addition to genetic" is called "methylation." It refers to an application of a methyl chemical group to a site on the DNA sequence that causes the gene not to be actuated; it remains silent. There may be many other epigenetic processes, but only two others have been scientifically delineated. Histone acetylation refers to an opening in a particular chromosomal region that promotes the expression of genes, whereas deacetylation closes the region to be more compacted and inactive. RNA interference relates to the RNA molecules produced from DNA (i.e., messenger RNA) binding back to the DNA at certain sites, deactivating gene expression. There may be many other epigenetic mechanisms yet to be discovered (39).

Each epigenetic change is referred to as a "mark." The total number of marks is termed the "epigenome." Once in motion, the epigenome can be "inherited," but, importantly, the possibility of modification is still extant. The salient point, however, is that these epigenetic processes can be actuated by environmental events such as diet, stress, medications, and perhaps even types of psychotherapy.

26.6.6. Epigenetic Effects from Adverse Environmental Experiences

Environmentally, studies indicate that rodents deprived of adequate maternal nurturing show a methylation of the component of the glucocorticoid receptor gene within the hippocampus that regulates cortisol. The impact of the environmental deprivation, for example, alters gene expression and affects cortisol production in the brain structure involved in learning and memory. The result is a lasting effect on *hippocampal* development and a reduced capacity for dealing effectively with subsequent stressful events (40).

Analogous findings in humans were reported by Champagne and Mashoodh (38) in which increased methylation of the cortisol regulation gene (assessed via analysis of cells extracted from fetal umbilical cord blood) was related to negative emotional conditions in maternal caregivers during pregnancy. This finding was associated with maladaptations by offspring in response to stressors, 3 years in the future (41). Thus, the emotionality of the mother resulted in an epigenetic change of a regulation gene, and that same change (epi-mutation) was passed on to offspring.

Environmental encounters experienced by a pregnant mother may have an effect on the developing fetus, the impact of smoking tobacco, for example, and other teratogens. Moreover, such effects may actually have an impact on fetal germ cells, with ramifications for generations to come. Seay (42) summarizes data indicating influences on gene expressions (redacting or activating) without modifications of DNA itself. High-fat diets in pregnant rodents, for instance, can alter methylation patterns affecting fetal germ cells leading to cancer susceptibility with generational implications. At the human level, obese fathers were found to carry a methyl "tag" leading to methyl alteration of a gene in their offspring with potential health ramifications.

26.6.7. Epigenetics and Neuropathology

Here are some of the exciting recent developments with respect to the emerging field of pathogenesis and the epigenome:

Alzheimer's disease: Investigations of epigenetic aspects of Alzheimer's disease support the general hypomethylation of genes that can compromise functioning in the medial temporal lobe. Studies of dietary modifications (i.e., markedly increasing ingestion of methyl groups such as vitamins B6 and B9, as well as acetylcarnitine) have even suggested significant cognitive improvements in patients in the early stages of the disease (43, 44).

The CACNA1C gene: As previously discussed, this gene has known epigenetic regulation via methylation patterns at CpG sites (45). As mentioned, the importance of calcium signaling for neurodevelopment cannot be overemphasized. Calcium influx through voltage-gated calcium channels regulates synaptic plasticity (related to learning), neurocircuitry involved in emotional processing, several executive functions, neurotransmission, and neuron growth (among many other functions). It is not difficult to see how abnormal regulation of the CACNA1C gene can affect the symptomatology observed in the several disorders evaluated in the monumental study of Nishioka et al. (45).

Schizophrenia: In addition to the recent work regarding calcium channeling, the focus of research has been on the protein reelin. This protein is found in neurons containing GABA and is important in the formulation and modulation of neuronal connections. GABA is the major inhibitory neurotransmitter in the central nervous system. Postmortem studies have found significantly reduced concentrations of reelin in the brains of schizophrenic patients attributable to hypermethylation of the reelin gene. One hypothesis is that a reduction of reelin in the GABA-containing neurons causes disruptions in neuronal circuits mediated by GABA that in turn disturbs higher neural functions (46).

Graff et al. (37) reviewed data suggesting both epigenetic effects on neurons and oligodendrocytes (glial or support cells) in schizophrenia and implicated again the hypermethylation of the reelin promoter that decreases reelin gene expression. Moreover, they indicate both hypermethylation of the GABAergic system and hypomethylation involving the dopaminergic system, resulting in prefrontal difficulties with attention and working memory impairments. The latter involves an increased activation of an enzyme (catechol-O-methyltransferase or COMT) that degrades dopaminergic neurotransmitters in the prefrontal area. Hypomethylation pertaining to COMT has been documented in the frontal lobe of schizophrenic patients and is associated with increased activation of the gene.

For greater technical detail, Abdolmaleky, Shafa, Tsuang, and Thiagalingam (47) present the most recent review of what is known and conjectured about enzymes that pertain to epigenetic modifications as well as epigenetic ramifications of commonly prescribed and experimental psychiatric medications and various vitamins and nutrients.

26.7. Epigenetics: Future Projections

The epigenome is the controlling "software" for DNA expressions that affect neurodevelopment and also pathogenesis. In the current state of knowledge, at least some of extant adverse epi-mutations can be modified by environmental interventions that include dietary changes, radiation, and, importantly, medications that explicitly target the molecular "switches" (e.g., methylation, acetylation; RNA interference) for activating and silencing DNA. There may be numerous additional epigenetic processes yet to be discovered. The promise for the future is the increasing use and evaluation of psychiatric drugs based on their epigenetic impact. The result may eliminate the guesswork and ambiguity regarding how medications affect the biochemistry and other forms of DNA expressions in the brain—from the environment to the epigenome, to the DNA, and eventually to cellular functions. That is, the future likely involves a stronger biologism as a foundation for the medical practice of psychiatry. Thus far, epigenetic medication successes have been reported for the DNA methyltransferase (DNMT) inhibitor "5-Asi" and the histone deacetylase inhibitor valproate for ameliorating reduced reelin, as well as the methyl donor "S-adenosyl methionine" pertaining to the epigenetic regulation of aggression (47, 48).

We have documented the effects of deleterious social conditions on the epigenome and hence on neurodevelopment. We have also documented the impact of a stimulating environment on brain development, structures, and functions. There are now several psychosocial interventions called "psychotherapy," some of which have bona fide effectiveness. These are the evidence-based treatments. One of the best substantiated of these is cognitive-behavioral treatment for anxiety disorders. Besides effectiveness at the behavioral symptomatology level, there are also effects on brain biochemistry. For instance, Cervenka (49) reported increased dopamine-binding receptors in the prefrontal cortex and hippocampus in patients following cognitive-behavioral therapy for social anxiety. These dopaminergic changes correlated with the manifestation of reduced anxiety states. It seems reasonable to posit that the environment involving trained therapists implementing procedures for modifying thinking and anxious behaviors together with the qualities of a therapeutic interpersonal relationship may have affected neurotransmitter improvements in the limbic system of the brain through epigenetic dynamics. A study linking a psychotherapeutic environment to the epigenome has yet to be conducted, but the requisites are in place including credible hypotheses concerning the epigenome. The simplest hypothesis relates to cognitive-behavior therapy modifying the methylation status (i.e., hypermethylation) of the promoter region of the gene (DRD2) that encodes the dopamine receptor (50).

In sum, the trends and trajectories of the pertinent research reviewed extrapolate to a possible future in which a psychiatric nosology has a more solid basis in known brain pathology, one in which prevention strategies are geared toward amelioration of documented determinants of abnormal brain structures and neurocircuitries. We can envisage a future with primary prevention occurring, at least in part, at a genetic level with secondary prevention aimed at modifying the epigenome from the effects of deleterious environmental influences. We can foresee a more efficient role for psychiatric medications selected on the basis of their known effects on brain physiology and the epigenome. Further, we can cognize a time epoch when the effectiveness of psychiatric interventions, including psychotherapies, is evaluated rigorously by measured changes in how the brain works.

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27
Catatonia in Psychiatric Illnesses

Dirk M. Dhossche, M.D., Ph.D., Lee Elizabeth Wachtel, M.D., Michal Goetz, M.D., Ph.D., and Pascal Sienaert, M.D., Ph.D.

Abstract Increased interest in the demarcation of catatonia from other conditions such as schizophrenia and autism is shown in the new DSM-5 category Catatonia Not Elsewhere Classified (NEC) encompassing catatonia of uncertain origin or associated with developmental conditions. Catatonia NEC is an imminently relevant diagnosis in patients who meet criteria for catatonia but without clearly defined associated psychotic, affective, or medical disorders. Catatonia NEC should be considered when catatonic symptoms present in patients with autism spectrum disorders, developmental disorders such as Prader-Willi Syndrome and Down Syndrome, tic disorders and Tourette Syndrome, Kleine-Levin Syndrome, aseptic encephalitis such as Anti-*N*-methyl-D-aspartate Receptor encephalitis, Pervasive Refusal Syndrome, or complex posttraumatic conditions.

Current experiences continue to support the use of benzodiazepines and ECT in catatonia as safe and effective treatments without the risk of worsening catatonia or precipitating Neuroleptic Malignant Syndrome as opposed to when antipsychotic medications are used as first-line or sole treatment

Historical and contemporary clinical and experimental catatonia models are available for future research, focusing on motor circuitry dysfunction, abnormal neurotransmitters, epileptic discharges, genetics, neuroendocrine and immune abnormalities, fear reactions akin to the animal defense strategy of tonic immobility, and developmental risk factors.

There have been advances in demarcating catatonia in a wide variety of patients as a treatable condition that requires prompt identification. Catatonia NEC in DSM-5 is likely to improve proper diagnosis and treatment of catatonia and to intensify research of this condition.

Keywords Catatonia • Malignant • Psychomotor abnormalities • Movement disorders • Schizophrenia • Mood disorder • Psychosis • Autism spectrum disorders • Developmental disorders • Tourette syndrome • Tics • Self-injury • Autism • Kleine-Levin Syndrome • Anti-*N*-methyl-D-aspartate Receptor encephalitis • Posttraumatic stress disorder • Neuroleptic Malignant Syndrome • Toxic Serotonergic Syndrome • Delirium • Children and adolescents • Benzodiazepines • Electroconvulsive treatment (ECT) • Autonomic symptoms • Vagal nerve

D.M. Dhossche, M.D., Ph.D. (✉)
Professor, Department of Psychiatry, University of Mississippi Medical Center, Jackson, MS, USA
e-mail: dirkdhossche@gmail.com

L.E. Wachtel, M.D.
Associate Professor, Department of Psychiatry, Johns Hopkins University, School of Medicine; Medical Director, Neurobehavioral Unit, Kennedy Krieger Institute, Baltimore, MD, USA
e-mail: wachtel@kennedykrieger.org

M. Goetz, M.D., Ph.D.
Assistant Professor, Department of Child Psychiatry, University Hospital Motol, Charles University, Prague, Czech Republic
e-mail: michal.goetz@lfmotol.cuni.cz

P. Sienaert, M.D., Ph.D.
Assistant Professor, Department of Psychiatry, University Psychiatric Center – Catholic University of Leuven, campus Kortenberg, Kortenberg, Belgium
e-mail: pascal.sienaert@uc-kortenberg.be

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And the more you really see mental patients and get to know their symptoms, the more you will be convinced that finally nothing else can be found and observed but movements and the whole pathology of mental patients consists of nothing else but the peculiarities of their motor behavior.

Carl Wernicke, 1900 (1)

It happens quite often that we fail to see something because it's too big.

Multatuli (pseudonym of Eduard Douwes Dekker; Dutch writer; 1820–1887)

27.1. Introduction

Catatonia is a unique syndrome characterized by specific motor signs, at times life-threatening when aggravated by autonomic dysfunction and fever, but treatable with benzodiazepines and electroconvulsive therapy (ECT) if recognized early (2, 3). Identifiable motor signs are immobility sometimes alternating with excessive motor activity that is mostly purposeless and not influenced by external stimuli, extreme negativism, reduced speech or muteness, repetitive movements (stereotypy), echolalia, echopraxia, and other peculiarities of voluntary movement. Tics and other sudden and non-rhythmic movements, often with self-injury, occur commonly in catatonic patients and may qualify as additional catatonic symptoms (4, 5).

Since the publication of the first version of this chapter in 2008, catatonia has been further delineated across a wide range of disorders (6, 7). An update on symptoms, prevalence, evaluation, treatment, risk factors, and experimental models of catatonia is presented, through review of literature and case-reports since 2008, incorporating important changes in the classification of catatonia that have been made in DSM-5 (8) (Table 27.1).

Table 27.1 Definition of catatonic symptoms.

Excitement	Extreme hyperactivity, constant motor unrest which is apparently non-purposeful
Immobility/stupor	Extreme hypoactivity, immobility. Minimally responsive to stimuli
Mutism	Verbally unresponsive or minimally responsive
Staring	Fixed gaze, little or no visual scanning of environment, decreased blinking
Posturing/catalepsy	Maintains posture(s), including mundane (e.g., sitting or standing for hours without reacting)
Grimacing	Maintenance of odd facial expressions
Echopraxia/echolalia	Mimicking of examiner's movements/speech
Stereotypy	Repetitive, non-goal directed motor activity (e.g., finger-play, repeatedly touching, patting or rubbing self)
Mannerisms	Odd, purposeful movements (hopping or walking tiptoe, saluting passers-by, exaggerated caricatures of mundane movements)
Verbigeration	Repetition of phrases or sentences
Rigidity	Maintenance of a rigid position despite efforts to be moved
Negativism	Apparently motiveless resistance to instructions or to attempts to move/examine the patient. The patient does the opposite of the instruction
Waxy flexibility	During reposturing, patient offers initial resistance before allowing himself to be repositioned (similar to that of bending a warm candle)
Withdrawal	Refusal to eat, drink, and/or make eye contact
Impulsivity	Patient suddenly engages in inappropriate behavior (e.g., runs down the hallway, starts screaming, or takes off clothes) without provocation. Afterwards, cannot explain
Automatic obedience	Exaggerated cooperation with examiner's request, or repeated movements that are requested once
Passive obedience (mitgehen)	Raising arm in response to light pressure of finger, despite instructions to the contrary
Gegenhalten/Counterpull	Resistance to passive movement that is proportional to strength of the stimulus; response seems automatic rather than willful
Ambitendency	The patient appears stuck in indecisive, hesitant motor movements
Grasp reflex	Strike open palm of patient with two extended fingers of examiner's hand. Automatic closure of patient's hand
Perseveration	Repeatedly returns to the same topic or persists with same movements
Combativeness	Usually in an undirected manner, without explanation
Autonomic abnormality	Abnormality of temperature (fever), blood pressure, pulse rate, respiratory rate, inappropriate sweating

27.2. Catatonia NEC: A Dark Horse in DSM-5

Catatonia was originally described in 1874 by Kahlbaum as a separate brain disorder with a cyclic, alternating, and ultimately progressive course (9). Kraepelin viewed catatonia as an exclusive subtype of dementia praecox or schizophrenia. In contrast, recent studies show the preponderance of underlying affective symptoms and syndromes, particularly mania, in adult catatonic patients (10–13) and comorbidity with an expanding list of adult and pediatric conditions (Table 27.2). Examples of catatonia are provided in Figs. 27.1–27.4.

In DSM-IV (44), catatonia was a specifier of Schizophrenia, Primary Mood Disorder, and Mental Disorder due to a General Medical Condition. However, major changes have been made in DSM-5 (8) including the deletion of catatonia as a type of schizophrenia, the creation of a new class of Catatonia Not Elsewhere Classified (NEC), and the addition of a catatonia specifier for 10 primary diagnoses. A uniform list of catatonia signs was adopted across all categories. Catatonia Secondary to a general Medical Condition created in 1994 has been retained.

TABLE 27.2 Disorders in which catatonia can emerge.

Developmental disorders
Autistic disorder (14–17)
Childhood disintegrative disorder (18, 19)
Mental retardation (20) including Down syndrome (21)
Prader-Willi syndrome (22)
Medical and neurological disorders
Catatonia due to a general medical condition (brain structural damage, seizures, metabolic, endocrine, and autoimmune disorders) (23–27)
Psychiatric disorders
Psychotic disorders (28)
Mood disorders (28)
Substance-induced disorders (23)
Medication-induced movement disorder (NMS) (29, 30)
Tourette syndrome (4, 17, 31)
Miscellaneous conditions
Anti-NMDA (*N*-methyl-D-aspartic acid) receptor encephalitis (32–36), PANDAS (Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections) (24, 26), encephalitis lethargica (37), and other aseptic encephalitides (38)
Kleine-Levin syndrome (19)
Psychogenic catalepsy (39)
Anaclitic depression (40, 41)
Pervasive refusal syndrome (42, 43)

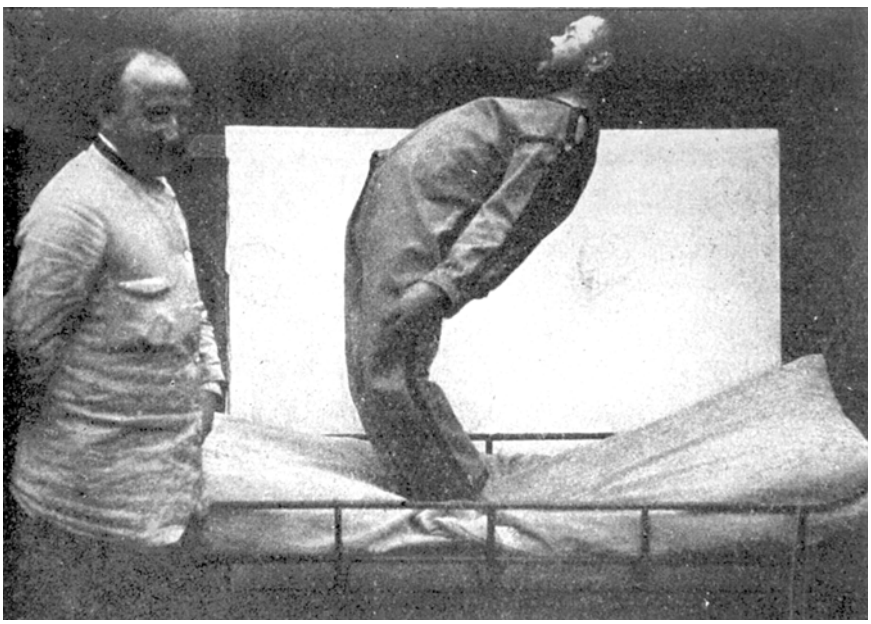

FIGURE 27.1 Catatonic rigidity (from reference 155, p. 267).

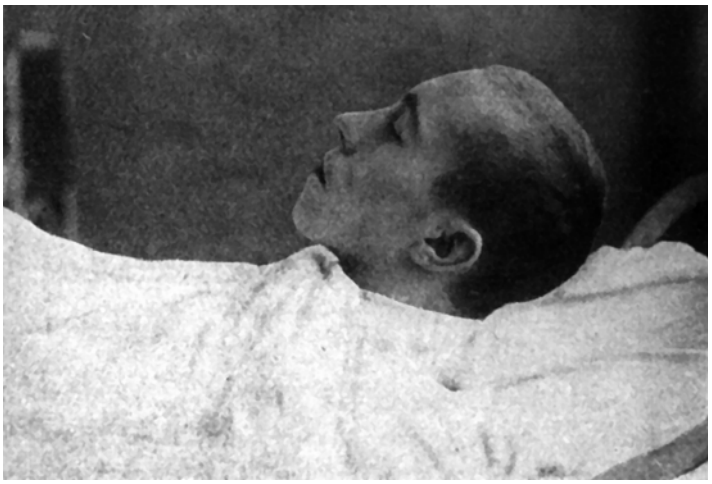

FIGURE 27.2 Catatonic rigidity ("pillow sign") (from reference 155, p. 269).

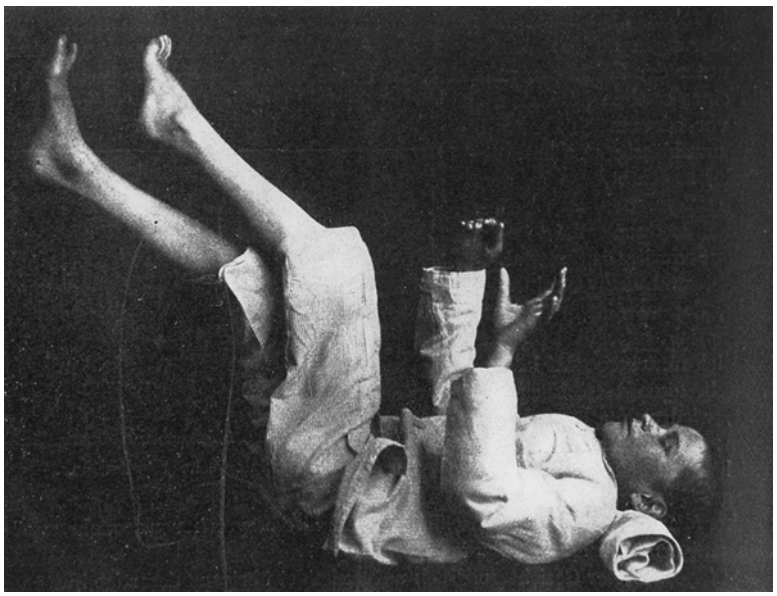

FIGURE 27.3 Flexibilitas cerea (from reference 155, p. 270).

FIGURE 27.4 Flexibilitas cerea (from reference 155, p. 272).

TABLE 27.3 Comparison between (malignant) catatonia and anti-NMDAR encephalitis.

	Catatonia	Anti-NMDAR encephalitis
First described by	Kahlbaum in 1874 (9) (catatonia) and Stauder in 1934 (50) (lethal or malignant catatonia)	Dalmau in 2007 (47)
Symptoms		
Abnormal movements	++	++
Autonomic dysfunction	++	++
Seizures	+	++
Risk factors		
Teratomata (ovarian)	-	++
Neoplasmata	+	+
Viral infections	+	+
Antipsychotics	++	?
Treatment		
Benzo's/ECT	++	?
Immune treatments	?	++

The recommendation for catatonia as an independent syndrome in the form of a separate category Catatonia NEC is profound and finalizes the divorce between catatonia and schizophrenia, in order to allow experience to refine the place of catatonia in clinical care and to offer the recommended treatments for catatonia to a wider range of patients. The known experience finds about 80% of the patients with catatonia respond to the benzodiazepines, and almost universal response to ECT in those who fail benzodiazepines. Prompt recognition of catatonia and in some cases treatment with ECT is likely to prevent medical complications, such as deep vein thrombosis, pulmonary emboli (45, 46), dehydration, malnutrition, and physical exhaustion.

The designation of catatonia specifiers for 10 primary diagnoses and the retention of a Catatonia Secondary to a Medical Disorder sustain the secondary position of catatonia in the prior classifications and do not encourage the first-line use of benzodiazepines in patients who meet the criteria for catatonia thereby continuing to create treatment dilemmas.

For example, the distinction between Catatonia Secondary to a Medical Disorder and Catatonia NEC is unclear. A case-in-point is the patient who meets criteria for (malignant) catatonia and tests positive for anti-NMDA receptor antibodies. Is the patient suffering from the newly coined anti-NMDAR encephalitis (47) that should be treated with immune treatments? Or is the patient suffering from malignant catatonia that should be treated swiftly with benzodiazepines and ECT? The enthusiasm for the newly defined disorder of anti-NMDA receptor encephalitis should not be a barrier for treating the recognized catatonia vigorously (32). The immune treatments that are recommended for the newly proposed form of synaptic autoimmune encephalitis often yield equivocal results, especially in pediatric cases. The sharp increase in the number of reports of pediatric cases of anti-NMDA receptor encephalitis highlights that catatonia is common yet often unacknowledged in children and adolescents (6, 19). There are now a few reports that show the efficacy of treatment with high-dose benzodiazepine and ECT in anti-NMDA receptor encephalitis (36, 48, 49). Studies comparing benzodiazepines or ECT with immune therapies in children, adolescents, and adults who meet criteria for catatonia and who test positive for the anti-NMDA receptor antibody are warranted (Table 27.3).

27.3. Evaluation, Differential Diagnosis, and Treatment

Catatonia should be considered in any patient when there is a marked deterioration in psychomotor function and overall responsiveness. Observation and psychiatric interview will not suffice to detect the catatonic syndrome, since the most striking symptoms such as posturing, are present only in a minority of the cases. It is of importance to elicit specific catatonic signs (such as negativism, automatic obedience, passive obedience, gegenhalten, or grasp reflex) during a neuropsychiatric examination. A rating scale or checklist may aid the detection and quantification of catatonia. Up to date, 6 different catatonia rating scales have been published: the Rogers Catatonia Scale (51), the Bush-Francis Catatonia Rating Scale (52), the Northoff Catatonia Rating Scale (53), the Braunig Catatonia Rating Scale (54), the Bush-Francis Catatonia Rating Scale Revised Version (55) and the Kanner Scale (56). Characteristics of these scales are presented in Table 27.4.

Reflecting different underlying diagnostic concepts, current diagnostic rating scales differ substantially in the nature and number of the items included. The total number of items ranges from 18 to 40. Both sensitivity and specificity of current rating scales is high. With the exception of the MRS-C, all rating scales provide a threshold score for the diagnosis of catatonia, based on the total score of the scale or on the score of a screening instrument, as in the BFCRS and the Kanner scale. Probably, not all scales are suited for use in the divergent patient groups in which catatonia can be encountered: the RCS is designed to detect catatonia in depression, whereas the MRC may be better suited in schizophrenia. None of the scales have been applied to autis-

TABLE 27.4 Overview of catatonia rating scales.

Dimension	MRS-C	RCS	BFCRS	NCRS	BCRS	Kanner
Screening instrument	No	No	First 14 items	No	No	11 items
Catatonia definition	?	>7	≥2 items of the screening instrument	1 item of each category and total score > 7	4 criteria with score ≥2	≥2 items of the screening instrument
Number of items	18	22	23	40 (13 motor, 12 affective, 15 behavioral)	21 (16 motor, 5 behavioral)	18
Range of item scores	0–2	0–2	0–3	0–2	0–4	0–8
Total scores	0–36	0–44	0–69	0–80	0–84	0–144
Procedure	Standard motor examination	Standard motor examination	Standard procedure	?	Semistructured examination	Semistructured examination
Inter-rater reliability (Correlation coefficient)	?	0.81	0,93 (0,95 BFCSI)	0.80–0.96	>0.83	?
Inter-rater reliability (Cohen's Kappa)	0.87	?	0.73 (0.83 BFCSI)	0.81	?	?
Test-retest reliability	0.67	0.89	?	0.80–0.95	?	?
Validity	?	Sens. and spec. 100% to DSM-IV in depressive subgroup	Sens. 100%, spec. 75–100% to older criteria	Sens. and spec.100% to older scales and criteria	?	?

MRS-C = Modified Rogers Scale, Catatonia Subscale; RCS = Rogers Catatonia Scale; BFCSI=Bush-Francis Catatonia Screening Instrument; BFCRS = Bush-Francis Catatonia Rating Scale; NCRS = Northoff Catatonia Rating Scale; BCRS = Braunig Catatonia Rating Scale; Kanner = Kanner scale.
Adapted from (57), copyright (2011) with permission from Elsevier.

TABLE 27.5 Diagnostic criteria for catatonia as per Fink & Taylor (3).

Criterion A	Immobility, mutism, or stupor of at least one hour duration, associated with at least one of the following: catalepsy, automatic obedience, or posturing, observed or elicited on two or more occasions.
Criterion B	Two or more of the following, which can be observed or elicited on two or more occasions: stereotypy, episodes of frenzied agitation, echolalia/echopraxia, waxy flexibility, automatic obedience, posturing, negativism, or ambitendency.

tic populations. The BFCRS, the BCRS and the Kanner scale are completed during a semi-structured interview. A correct BCRS examination is time consuming, whereas completing the BFCRS is easily integrated in a psychiatric evaluation, making the BFCRS a practical screening tool for routine clinical practice. Current rating scales seem best suited for screening, offering the clinician a scheme to perform a neuropsychiatric examination and improving the detection of catatonic symptoms. These scales are less well suited for assessing severity and change, since they lack the sensitivity necessary to measure change (58).

Although different criteria for a diagnosis of catatonia are used, we find the criteria proposed by Fink & Taylor (3) relevant and practical (Table 27.5). In DSM-5, catatonia is diagnosed when three or more of a list of 12 catatonic symptoms are present (8). The 12 catatonic symptoms are: stupor, catalepsy, waxy flexibility, mutism, negativism, posturing, mannerism, stereotypy, agitation (non-influenced by external activity), grimacing, echolalia, and echopraxia.

27.3.1. Differential Diagnosis

A detailed history, clinical examination, and application of diagnostic criteria must be used to differentiate catatonia from other well-recognized conditions, syndromes, or disorders featuring psychomotor abnormalities that may overlap with the manifestations of catatonia. Making an adequate differential diagnosis of catatonia is complicated by the fact that there is no biologic marker diagnostic of catatonia. The differential diagnosis of catatonia when motor activity is increased or reduced is shown in Table 27.6.

Some motor manifestations of catatonia such as catatonic excitement, psychomotor retardation, or negativism may be mistaken for purposeful, oppositional and attention-seeking behaviors that are under full control of the patient and for secondary gain. Decreased speech, muteness, or posturing may be mistaken as indicative of conversion disorder especially when following stressful events or trauma. It may be very difficult in some instances to determine the origin of these behaviors and

TABLE 27.6 Differential diagnosis of catatonia.

Differential diagnosis; when increased motor activity
Acute dystonia
Tardive dyskinesia
Akathisia
Withdrawal-emergent dyskinesias
Tics/Gilles de la Tourette
Purposeful, oppositional, or attention-seeking behaviors
Conversion disorder
Compulsions (in obsessive-compulsive disorder)
Epilepsy
Delirium
Differential Diagnosis; when reduced motor activity
Parkinsonism and Parkinson's disease
Malignant hyperthermia
Neuroleptic malignant syndrome
Toxic serotonergic syndrome
Epilepsy
Selective mutism
Conversion disorder
Purposeful, oppositional, or attention-seeking behaviors
Status epilepticus
Delirium
Coma

FIGURE 27.5 Portrait of Karl Ludwig Kahlbaum, M.D., (1828–1899).

degree of control that the patient has on these behaviors, even during longer periods of observation. The catatonia benzodiazepine challenge test that will be discussed in the treatment section may be useful in such situations. A profoundly positive response would support a diagnosis of catatonia, although the therapeutic effects of anxiolytics including amytal and benzodiazepines as diagnostic tools and treatment are also known in conversion disorders (59–63). A negative challenge test is expected when motor abnormalities represent voluntary behaviors for secondary gain although there may be mild improvement due to specific sedative effects.

Epilepsy and status epilepticus are important differential diagnoses given the overlap of symptoms between psychomotor seizures and catatonia and the increased prevalence of seizures in catatonic patients (3). In his original description, Kahlbaum (Fig. 27.5) reported seizure-like symptoms in catatonia (9). Seizures are also frequent in children and adolescents with autism (64, 65) and catatonia (7, 20). Seizures and catatonia are not mutually exclusive in this population. However, frank epileptic activity is usually absent in EEG recordings in catatonic patients. Typical findings in catatonia include diffuse slowing in patients in catatonic stupor and a dysrhythmic EEG in catatonia. These findings are consistent with non-convulsive status epilepticus that

resolves when catatonia remits and is consistent with the underlying theory (66, 67) of this disorder, that there is localized brain excitation in catatonic patients in specific deep brain structures that are not detected by current EEG techniques, which improves with anticonvulsant medications but especially with benzodiazepines and ECT.

27.3.2. Laboratory and Other Investigations

Various infectious, metabolic, endocrine, neurological, toxic and autoimmune conditions have been associated with catatonia and must therefore be assessed. Proposed basic investigations include a complete blood count and metabolic panel, erythrocyte sedimentation rate, magnetic resonance imaging, electroencephalogram, cerebrospinal fluid analysis, antinuclear antibodies, and urine and organic metabolic testing, with further testing based upon clinical findings (68) (Fig. 27.6).

A drug screen to detect common illicit and prescribed substances is necessary. Recreational drugs (phencyclidine, mescaline, psilocybin, cocaine, ecstasy, opiates and opioids), disulfiram, steroids, antibiotic agents (ciprofloxacin), baclofen and bupropion have been associated with the emergence of catatonia. Withdrawal of benzodiazepines, gabapentin and dopaminergic drugs, especially if done rapidly, has precipitated catatonia in some patients (3).

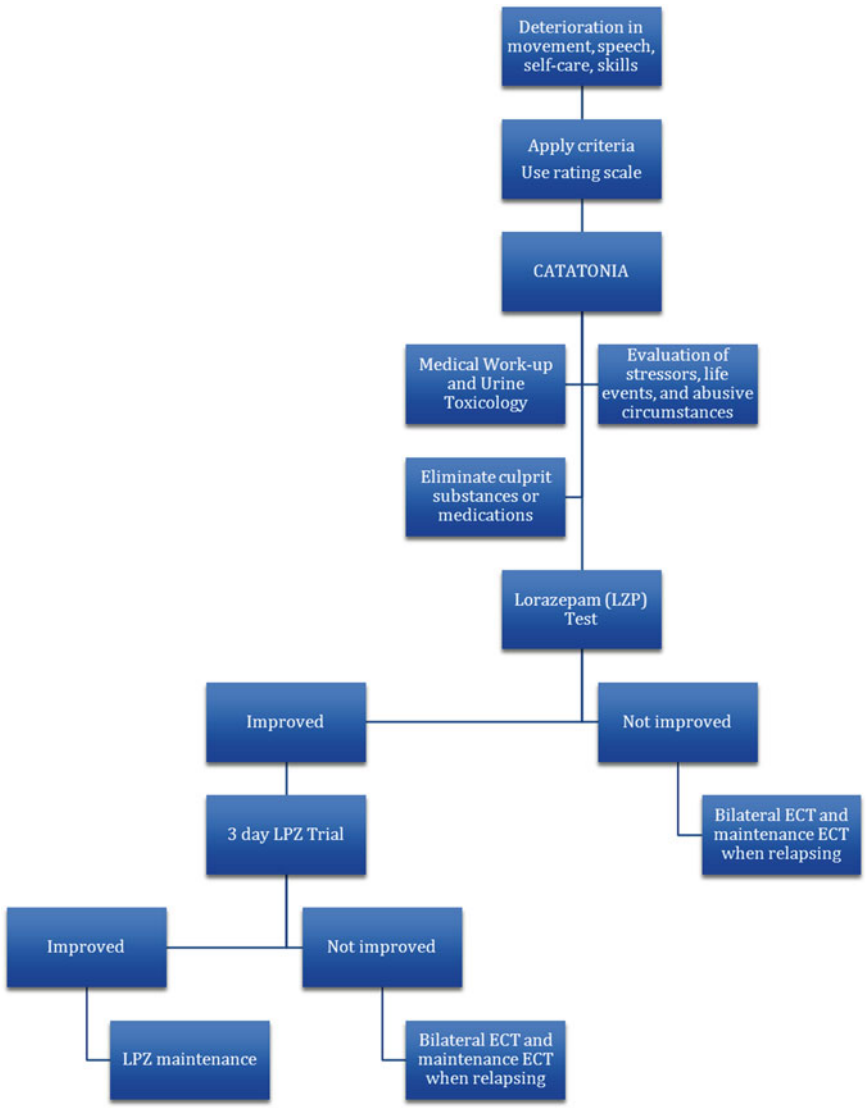

FIGURE 27.6 Assessment and treatment algorithm for catatonia.

27.3.3. Medication Management

All prescribed medications should be evaluated for their potential to induce catatonic symptoms, since many medications can cause catatonia or catatonia-like conditions. Antipsychotic agents, especially of the first generation, should be discontinued as they are contraindicated in patients who exhibit the signs of catatonia because of the reported increased incidence of malignant catatonia or neuroleptic malignant syndrome (NMS) in patients with incipient signs of catatonia (69, 70). The symptoms of malignant catatonia or NMS are essentially the motor symptoms of catatonia compounded with autonomic symptoms (fever, blood pressure abnormalities, hypoventilation, excessive sweating). NMS is considered a toxic reaction to psychotropic medications, particularly antipsychotics.

Once catatonia is resolved, second generation antipsychotics with low D2 blockade (quetiapine, olanzapine) or with D2 partial agonism (aripiprazole) should be preferred for treatment of residual psychotic symptoms, if any (71).

27.3.4. Medical Management

Simultaneous treatment of catatonia and a drug-induced or medical condition, if any is detected, is generally recommended in addition to supportive measures. For instance, despite the withdrawal of the offending agent, treatment of an underlying infection or metabolic disease, or the removal of a malignancy, as the case may be, catatonia often persists and requires urgent intervention that should not be postponed for elaborate searches for ill-defined or poorly treatable medical conditions. This may be particularly relevant in recent cases of presumed autoimmune entities such as Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal infections (PANDAS) and anti-NMDA-receptor encephalitis where catatonic symptoms are evident, yet well documented anti-catatonic treatments are rejected in favor of novel immunological interventions of questionable benefit and possible danger (32, 72).

27.3.5. Lorazepam Test Validates Catatonia

As a first step, a benzodiazepine challenge test of 1 or 2 mg of lorazepam that can be administered per os, intramuscularly, or intravenously, should be used to verify the catatonia diagnosis (Fig. 27.6) (2, 3, 73). If intravenous lorazepam is used, any changes in the next two to five minutes are noted. If no change is observed, the second 1 or 2 mg lorazepam is injected, and the assessment is repeated. The interval for the repeat dose is longer for intramuscular (15') and peroral (30') administration. The use of the gamma-aminobutyric acid-A (GABA) receptor modulator zolpidem has also been developed as an alternative catatonia challenge test and implemented, particularly in Europe (74). Zolpidem is only available in oral form.

When a single dose of lorazepam improves catatonia, lorazepam can be prescribed at regular intervals to maintain improvement. Many catatonic patients require relatively high dosages of lorazepam, occasionally up to 24 mg daily, for symptom resolution. Our experience shows that in some patients with catatonia doses up to 24 mg daily are tolerated without ensuing sedation, especially when instituted using daily incremental dosages, and result in marked reduction of catatonic symptoms. This suggests that in some cases, catatonia may be associated with high tolerance to benzodiazepines. Careful monitoring in a medical setting for excessive sedation, respiratory compromise, and other side effects is required.

27.3.6. Pre-ECT Laboratory and Other Investigations

Routine laboratory tests and an anesthesia consult are required during the pre-ECT work-up. Routine brain imaging studies is not generally recommended prior to ECT, however, in some hospitals, pre-ECT brain CT or MRI is mandatory. Additional consultation may be required in selected cases to stabilize general medical issues such as risk of dehydration and hemodynamic abnormalities in catatonic patients before starting ECT (Fig. 27.6).

27.3.7. ECT Parameters

The relief of catatonia often seems to require more frequent seizures than those necessary for the relief of major depression. The UK standard practice of two seizures a week, although effective for major depression, may not be so for catatonia. In severe or malignant catatonia, daily ("en bloc") treatment for three to five days may be necessary. Second, the efficacy of bilateral (bitemporal or bifrontal) electrode placement is better documented than is unilateral placement. Therefore, based on practical experience, the authors recommend bilateral electrode placement for catatonia. Furthermore, in our experience the number of treatments, before substantial and sustained improvement becomes obvious, cannot be predicted. Therefore, ECT treatment must be individually tailored and the duration and the frequency of treatment should be based on regular assessments, possibly after every 6–12 treatments.

27.3.8. ECT and Concurrent Medications

All psychiatric medications should be stopped prior to initiation of ECT, as well as any other non-psychiatric medications, if possible. An exception is when there was a partial response with benzodiazepine treatment, often administered in a high dose; in these instances, ECT and a benzodiazepine may be administered concurrently. Discontinuation or rapid taper of the benzodiazepine may not be advisable at the start of the ECT course, because of a risk of altering the seizure threshold. Concurrent use of lorazepam (or another benzodiazepine) and ECT is then a useful treatment variant. Intravenous administration of flumazenil, a benzodiazepine antagonist, can be used if lorazepam interferes with eliciting seizures during ECT and may be beneficial even if seizures outwardly appear adequate; indeed, use of flumazenil has also been proposed in benzodiazepine-naïve patients for augmentation of ECT effect (75).

27.3.9. Maintenance ECT in Catatonia

Maintenance-ECT (M-ECT) may be useful for sustained symptom-remission (76, 77). There are no studies which suggest evidence for structural or histopathological changes during M-ECT (78, 79). Studies of various cognitive functions also demonstrate a stability of various longitudinal cognitive measures (80–82).

Less information is available regarding M-ECT in patients with catatonia and autism. One case series (83) presents the M-ECT courses of three autistic catatonic patients who received up to 286 maintenance treatments with sustained remission of catatonia and without subjective evidence of decline in cognitive or adaptive skills. One patient was unable to access M-ECT for legal reasons and promptly relapsed into catatonia. While the number of M-ECT delivered to these patients appears high, this finding is considered within the context of a special patient population who are known to have a relatively poor response to psychotropic agents, and possibly a higher overall propensity for treatment resistance.

27.4. Malignant Catatonia and Related Conditions

Malignant catatonia is a severe form of catatonia, coined as “lethal catatonia” by Stauder (50) in 1934, that includes the constellation of catatonic signs, motoric excitement, stuporous exhaustion, autonomic instability, respiratory failure, collapse, coma and ultimately death. This malignant form of catatonia is of acute onset and systemically devastating requiring intensive medical care. Patients appear to have an acute infectious process leading to exhaustive but negative evaluations. Patients with malignant catatonia may present in both agitated and stuporous states (3). Untreated malignant catatonia is fatal in 10–20% of cases, with death ensuing within mere days of onset. Malignant catatonia also occurs in children and adolescents (84–87). Malignant catatonia should feature prominently in the differential diagnosis of the acute encephalopathies as a treatable syndrome with acute onset of unresponsiveness, muteness, echolalia, echopraxia, and other psychomotor abnormalities, along with fever and signs of autonomic instability.

Neuroleptic Malignant Syndrome (NMS) is a similar syndrome caused by typical as well as atypical antipsychotics and other psychotropic medications, and characterized by motor rigidity, lowered consciousness, autonomic instability, and fever. NMS is best considered malignant catatonia caused by administration of antipsychotic and other psychotropic agents; indeed, the physical and physiological symptoms as well as the laboratory indices, such as leukocytosis, elevated creatine phosphokinase, and decreased serum iron, show prominent correlation (2, 3). NMS responds to classic anti-catatonic treatments, i.e., benzodiazepines and ECT (2, 3, 69).

Toxic serotonin syndrome, malignant hyperthermia, and delirium constitute another group of disorders that are characterized by varying levels of hypokinesis and muscle stiffness, in combination with altered levels of consciousness and autonomic dysfunction. For example, there is discussion in the literature if toxic serotonin syndrome truly differs in key aspects with catatonia, or alternatively, if toxic serotonin syndrome should be regarded as another medication-induced form of catatonia (69, 88). Response of toxic serotonin syndrome to the same treatments as catatonia would strengthen the argument of relatedness. Malignant catatonia is similar to malignant hyperthermia in that both share muscular rigidity, hypermetabolic and hyperthermic states, yet the latter is uniquely associated with either succinylcholine usage or a genetic response to inhaled anesthetics (2, 3). A genetic model of hyperthermia is the Porcine Stress Syndrome, a congenital, autosomal recessive disorder which affects pigs, dogs, cats, and horses and is caused by a fundamental intolerance of stress due to a defective ryanodine receptor which affects closure of calcium channels in the sarcoplasmic reticulum and causing a sudden, sustained rise in intracellular calcium and consequent muscle contracture and up-regulation of metabolism (89).

Some patients diagnosed with delirium meet criteria for malignant catatonia (90, 91). Classifying these patients is difficult because DSM diagnostic rules state that catatonia should not be diagnosed if occurring exclusively during the course of a delirium while acknowledging that similar medical conditions of infectious, metabolic, endocrine and neurological etiologies

are associated with both catatonia and delirium (44). The validity of this DSM provision is uncertain given the lack of studies in the literature that have assessed the importance of catatonia during delirium. The issue is important because treatments for catatonia and delirium are different, albeit with overlap. While delirium is typically treated with (typical or atypical) antipsychotics, the emergence of catatonia in delirium may caution against the use of antipsychotic medications due to the aforementioned risk of worsening catatonia with antipsychotic medications (69, 70). There are no new guidelines regarding this issue in DSM-5, probably due to the lack of studies.

Another unresolved classification issue is whether catatonia should be included in the differential diagnosis in patients with coma (complete unresponsiveness) (92), and, in a similar vein, if stupor or profound unresponsiveness can be the sole presenting symptom of catatonia (92–94). Recent case-reports have shown that patients with levels of unresponsiveness similar as in coma, and without other catatonic symptoms (except resistance to eye-opening) responded to electroconvulsive therapy (95) and intravenous benzodiazepines (94).

27.5. Pediatric Catatonia

A previous literature review from 1966–1996 (20, 22) found 30 cases of catatonia in patients younger than 18 years of age. Several children and adolescents had underlying mental retardation or autism spectrum disorder. Benzodiazepines and ECT were the most reliable treatments, similar as reported in adult catatonia. Table 27.7 shows the frequencies of the most common catatonic symptoms in children and adolescents reported by Dhossche & Bouman (20, 22).

Since then, other cases have been published confirming that catatonia occurs in children and adolescents with associated psychotic, affective, drug-induced, or medical disorders, but also in patients with autistic, developmental, and tic disorders, and occasionally in children with no clearly identifiable medical or psychiatric conditions (4, 19).

Table 27.8 lists pediatric studies showing a wide variability of prevalence rates of catatonia in selected patient groups and settings, suggesting that catatonia may not be rare. Adolescents with catatonia comorbid with schizophrenia and affective dis-

TABLE 27.7 Catatonic symptoms in children and adults.

	Children	Adults
	%	%
Mutism	87	78
Posturing/grimacing	52	66
Stupor	80	66
Staring	49	57
Waxy flexibility	62	35

Adapted from (22), copyright (1997) with permission from Springer Science + Business Media.

TABLE 27.8 Prevalence of pediatric catatonia: review of the literature since 1992.

Authors (year)	Sample size	Design sample population	% with catatonia
Green et al. (1992) (97)	38	Prospective Childhood schizophrenia	32
Moise & Petrides (1996) (98)	13	Retrospective ECT	46
Wing & Shah. (2000) (99)	506	Prospective Autism	17
Thakur et al. (2003) (28)	198	Prospective Psychiatric clinics	18
Cohen et al. (2005) (100)	4976	Prospective Psychiatric clinics	0.6
Billstedt et al. (2005) (101)	120	Prospective Autism	12
Ohta et al. (2006) (102)	69	Prospective Autism	12
Consoli et al. (2009) (103)	199	Meta-analysis ECT	6
Ghaziuddin et al. (2012) (104)	101	Retrospective At-risk inpatients	18
Goetz et al. (unpublished)	92	Retrospective First-break adolescent psychosis	33

orders have a 60-fold increased risk of premature death, including suicide, when compared to the general population of same sex and age (96).

27.6. Catatonia in Autism Spectrum Disorders

Catatonia has been increasingly recognized as a comorbid syndrome of autism spectrum disorders, identified at a rate of 12–17% in adolescents and young adults with autism spectrum disorders (99, 101) and with other intellectual disabilities (22, 105). Catatonic symptoms, such as mutism, stereotypic speech, echolalia, stereotypic or repetitive behaviors, posturing, grimacing, rigidity, mannerisms and purposeless agitation feature prominently in autism. Therefore, only a sharp and marked increase in these symptoms, often in adolescence, qualifies for a diagnosis of catatonia (99, 106, 107).

In some cases, catatonia may be a feature of another major psychiatric syndrome such as depression (108), bipolar illness (109) or schizophrenia (110), yet many patients do not qualify for a clear diagnosis of mood or a psychotic disorder, often due to the fact that patients are nonverbal and have severe cognitive impairments. Case-reports also describe catatonia in pediatric patients with genetic disorders which are characterized by varying degrees of developmental impairment but the autistic features often do not amount to a full diagnosis of autism; catatonia has been reported in patients with Prader-Willi Syndrome (22) and Down Syndrome (111).

Most cases of catatonia in children and adolescents with autism spectrum disorders are not associated with underlying medical or psychiatric conditions. For example, in a sample of 58 children and adolescents with catatonia, 18 (31%) had a history of developmental disorder, i.e., autism spectrum disorder, intellectual disability or neurodevelopmental malformation (112). Only two of those had an identifiable underlying medical or psychiatric condition.

Two systematic studies show catatonia to occur in 12% to 17% of adolescents and young adults with autism spectrum disorders (99, 101). Wing & Shah report that 17% of a large referred sample of adolescents and young adults with autism spectrum disorders satisfied modern criteria for catatonia (99). Thirty individuals with autism spectrum disorders aged 15 years or older met criteria for catatonia, with classic Autistic Disorder diagnosed in 11 (37%), atypical autism in 5 (17%), and Asperger Disorder in 14 (47%). Under age 15, no child demonstrated the full syndrome although isolated catatonic symptoms were often observed. In the majority of cases, catatonic symptoms started between 10 and 19 years of age. Five individuals had brief episodes of slowness and freezing during childhood before age 10. Obsessive-compulsive and aggressive behaviors preceded catatonia in some. Visual hallucinations or paranoid ideas were occasionally reported, but no diagnosis of schizophrenia could be made. This study also emphasized additional symptoms of catatonia that may be particularly characteristic of catatonia in autism spectrum disorders, including amotivation, global slowness, and prolonged time to complete previously mastered tasks. It is important to recognize these additional symptoms along the catatonic spectrum, because they may otherwise be erroneously attributed to as oppositional or “stubborn” behavior.

In the second study, 13 (12%) of 120 autistic individuals, between ages 17–40 years, had clinically diagnosed catatonia with severe motor initiation problems (101). Another four individuals had several catatonic symptoms, but did not meet criteria for the full syndrome. Eight of the 13 individuals with catatonia suffered from classic Autistic Disorder; the remaining five were diagnosed with atypical autism. The proportion of those with Autistic Disorder that were diagnosed with catatonia was 11% (8/73). Fourteen percent (5/35) of those with atypical autism had catatonia.

A recent hospital-based study (104) of 101 child and adolescent psychiatric inpatients with "at risk" diagnoses including any autism spectrum disorder, psychotic disorder not otherwise specified, intermittent explosive disorder, mental retardation, neuroleptic malignant syndrome or previously diagnosed catatonia found that 18% of patients met criteria for catatonia, based upon three or more symptoms, including unexplained agitation or excitement, disturbed or unusual movements, reduction in movement, reduction or loss of speech and repetitive/stereotyped movements. The authors emphasized poor recognition of catatonia in these pediatric conditions, including, but not limited to, pervasive development disorders.

Functional regression in daily self-care, social and educational activities may also be a prominent feature of the catatonic presentation in autism. In many cases, the ability to self-feed, dress and bathe, or participate in previously mastered leisure and educational activities may be sharply compromised. Additionally, continence may be lost (22).

27.7. Post-traumatic Catatonia: The Ultimate Motor Response to Fear

Catatonia has been called “*the ultimate response to fear*” (113), representing a common final pathway in the response to impending doom, analogous to the animal defense strategy of tonic immobility or freezing (114). Tonic immobility is a last-ditch animal defense strategy against entrapment by a predator within a sequence of freezing-flight-fight-tonic immobility.

This notion is supported by observations that catatonia can develop after severe traumatic events in children and adolescents (115–117). For example, a recent case was reported of a 14-year-old-girl with severe catatonia precipitated by emotional turmoil due to cyber-bullying who was successfully treated with ECT and amantadine (118). In an epidemiologic study of 1098 adolescents, those who experienced bullying three or more times a month were 3.43 times as likely to report increasing psychotic experiences (119). The case-report extends findings that adolescent bullying increases the risk for psychotic experiences by linking cyber-bullying, an intrusive form of bullying, to onset of catatonia.

Shah & Wing (120) found that ongoing stressful experiences often precede the development of catatonia in autistic young adults. Life events, the loss of routine and structure, experiences of loss, conflicts with parents, caregivers, or peers, and discrepancies between the higher functioning autistic individual's capabilities and the expectations of parents, can precipitate catatonia.

Observations that catatonia follows overwhelming anxiety due to trauma or perceived danger, the positive response of catatonia to anxiolytics such as benzodiazepines or barbiturates, and psychogenic theories of catatonia (121) are particularly applicable to people with psychosis or autism spectrum disorders due to their increased social, cognitive, and sensory vulnerabilities (115, 122). It is recommended that patients with catatonia are assessed for traumatic and abusive events in family and broader environments in addition to medical causes for catatonia.

27.8. Mechanism of Catatonia

Although the etiology and pathophysiology of catatonia are unknown, findings about the occurrence of catatonia in a wide variety of conditions, including autism, suggests that the available models (66, 123) to study catatonia should be broadened to include models of developmental impairment.

Historically, the study of experimental catatonia in animals induced by bulbocapnine injections was introduced in 1928 by de Jong and Baruk (124). Bulbocapnine is an alkaloid resembling apomorphine, a dopamine agonist. Later mescaline was found to produce similar effects in animals, along with reserpine, adrenocorticotropic hormone (ACTH), and chlorpromazine. Baruk also described hypopituitary, hepatic, and asphyxia models of catatonia. Table 27.9 shows an overview of tentative clinical (66) and corresponding experimental models.

An appropriate focus is the area of stereotypic or repetitive movement abnormalities which are considered cardinal symptoms of several disorders including catatonia, autism, stereotypic movement disorder, and tic disorders (when tics are viewed as sudden and non-rhythmic variants of stereotypy) (4, 130). Motor stereotypy constitutes a separate domain with increasing evidence of a neurobiological mechanism involving neuroadaptations in cortico-basal ganglia pathways arising from the interplay of genetic and experiential factors (125, 131).

Catatonia has been associated with Prader-Willi Syndrome (PWS), a genetic disorder arising from the lack of expression of genes on the paternally derived chromosome 15q11-q13 (22, 105). The behavioral phenotype of PWS consists of catatonic symptoms, stereotypies, compulsive self-injury, excessive sleepiness or unresponsiveness, and psychosis. The abnormal pattern of expression of sex-specific imprinted genes on 15q11-13 (containing a cluster of $GABA_A$ receptor subunit genes) may increase risk for catatonia in PWS.

Several lines of evidence suggest the importance of neuroendocrine abnormalities in catatonia. A clinical endocrine model is provided by the Kleine-Levin Syndrome (KLS), a poorly understood syndrome, occurring mostly in male adolescents, that is characterized by recurrent episodes of excessive sleep, and behavioral abnormalities such as hyperphagia or hypersexuality, in which altered diencephalic function is considered a central feature. KLS has been proposed as a type of episodic adolescent-

TABLE 27.9 Clinical and animal models for catatonia, immobility, catalepsy, and stereotypy.

Catatonia model	Clinical model	Animal model
Motor circuitry dysfunction	Stereotypical movement disorders	Dopamine agonists (e.g., apomorphine) injections in rat striatum (125)
Epilepsy	Nonconvulsive status epilepticus	Pentylenetetrazol injections in rats (126)
Genetic	Prader-Willi syndrome	Mutant mouse model for human 15q11-13 duplication (127) and porcine stress syndrome (89)
Neurotransmitter	Neuroleptic malignant syndrome	Drug-induced catalepsy induced by bulbocapnine (124), reserpine, ketamine, or typical antipsychotics
Endocrine	Kleine-Levin syndrome Prader-Willi syndrome	Hormonal induction of catatonia by adrenaline, acetylcholine, and ACTH (124)
Immune	Autoimmune (limbic) encephalitis	Lipopolysaccharide-induced chronic inflammation in rats (128)
Fear reaction	Reactive catatonia	Tonic immobility in various animals (114)
Developmental	Autistic regression	Prenatal exposure to valproic acid in rats (129)

onset catatonia based on the symptom overlap between KLS and catatonia and on the profound response of all symptoms, including "hypersomnia", to lorazepam (19).

The overlap between catatonia and pediatric autoimmune (limbic) encephalitis (32, 36) suggests involvement of autoimmunity and cerebral antibodies. There are now a few reports that show the efficacy of treatment with high-dose benzodiazepine and ECT in the recently coined and purportedly autoimmune anti-NMDA receptor encephalitis (36, 48, 49).

The finding that severe trauma may precipitate catatonia raises questions about mechanisms by which trauma leads to catatonia or other disorders. The biological pathways of early trauma leading to psychiatric and medical disorders are thought to encompass endocrine, immune, electrophysiological, and neuropsychological factors as well structural changes in the developing brain (132–136). The likely involvement in catatonia of central GABA function and its major role in central integration of hypothalamic-pituitary-adrenal stress responses in the basal forebrain and hypothalamus (137) is an important lead for future clinical and experimental studies assessing early trauma as contributing to the development of catatonia.

A speculative model concerns developmental catatonia, i.e., the occurrence of catatonia in young children causing over time irreversible psychopathology similar to autistic impairment (138, 139). Prenatal exposure to valproic acid (VPA) is a promising animal model of early-onset catatonia that has also been studied as a model for autism (129). Offspring of female rats injected with VPA on day 12.5 of gestation show brain abnormalities including smaller cerebella with fewer Purkinje cells. The rats exhibit catatonic-like behaviors appearing before puberty that include lower sensitivity to pain, diminished acoustic prepulse inhibition, repetitive hyperactivity, unresponsiveness and withdrawal.

27.9. Novel Vagal Theory of Catatonia

Although catatonia is considered primarily a motor syndrome, forty percent of catatonic patients show autonomic symptoms including abnormalities of temperature, blood pressure, pulse rate, respiratory rate, and perspiration (3, 22). Forty-five percent of pediatric cases show urinary-fecal incontinence (22), another feature of autonomous dysfunction. Some cases show bradycardia (94, 140) and bronchorrhea (141), indicative of strong vagal activity. Autonomic dysfunction is the hallmark of malignant catatonia (2, 3), its drug-induced variant Neuroleptic Malignant Syndrome (142), and aseptic encephalitis with catatonic symptoms, including the recently coined anti-NMDAR encephalitis (19, 32, 47). Early studies also support that there is autonomic dysfunction in catatonia (143, 144).

Autonomic abnormalities in catatonia support the image that catatonia represents a common end state response to feelings of impending doom across a wide range of medical and psychiatric disorders, finding its evolutionary counterpart in tonic immobility (114). Volchan et al. (145) found signs of tonic immobility, such as reduced body sway, increased heart rate, and diminished heart rate variability, in trauma-exposed patients with PTSD while listening to their autobiographical trauma, implying that tonic immobility is preserved in humans as an involuntary defensive strategy.

Autonomic dysfunction in catatonia implies involvement of the autonomic nervous system that consists of the parasympathetic subsystem, mediated by the vagus nerve, and the sympathetic subsystem, mediated by sympathetio-adrenal circuits in the spinal cord. A useful framework is the Polyvagal Theory that was first formulated by Porges in 1995 (146, 147).

The Polyvagal Theory poses that two different vagal branches control different behavioral responses to threat, and that a human immobility response with behavioral (stupor) and metabolic shutdown (increased sweating, hypoventilation, decreased peristalsis, urinary and fecal incontinence, and vasovagal responses) represents the most primitive response to perceived imminent danger when fight-flight reactions fail or are not available.

A separate set of unmyelinated vagal fibers projecting to the nucleus dorsalis of the vagal nerve is thought to mediate this response through efferent fibers to the diaphragm, heart, gastrointestinal tract, lungs, pancreas, and other visceral organs. This reflex is adaptive in reptiles but potentially lethal in humans. Catatonia resonates clearly in the description of the immobility response and yet is not recognized or acknowledged in the Polyvagal Theory as its clinical manifestation.

A *vagal theory of catatonia* (148) supports abnormalities in a wide range of functions, regulated by the efferent vagal nerve and associated with catatonia, encompassing brain electrical and motor circuitry function, neurotransmitters, neuroendocrine and immune function. Toxic and medical factors may also trigger catatonia through afferent vagal activation. It is an intriguing thought that the vagal nerve, whose fibers are eighty percent afferent, may also be involved in signaling, through its afferent pathways, information to the brain about "internal" (toxic, immune, infectious, metabolic) precipitants of catatonia. Studies support effects on vagal tone by benzodiazepines (149–151), zolpidem (152) (a non-benzodiazepine sedative that has been effectively used in catatonia) and ECT (153), as predicted and required by a vagal theory.

Studies are warranted into various aspect of autonomic dysfunction of catatonia. There is evidence that increased anxiety and arousal accompany the development of catatonia (115). These observations beg for more scrutiny, using modern techniques, along the lines of earlier studies (143, 144). A vagal theory intimates use of vagal nerve stimulatory techniques as novel treatments for catatonia. The Food and Drug Administration (FDA) approved intermittent stimulation of the left vagal nerve (Vagal

Nerve Stimulation; VNS) as adjunctive therapy for partial-onset epilepsy in July 1997 and for treatment-resistant depression in 2005. Improvement in the control of seizures has been well documented with VNS. The effects in treatment-resistant depression remain controversial. Non-epileptic benefits in the quality of life and changes in behavior have not been as well documented, except for the enhancement of short-term memory (154). Further studies need to assess if vagal nerve stimulation has any role in the treatment and relapse prevention of catatonia. Several patients require maintenance ECT for months and even years to avoid relapses into catatonia. Although maintenance ECT is safe and without neuropsychological sequelae in such patients, finding adjuvant or alternative preventive treatments would be very valuable.

27.10. Conclusions

There have been advances in demarcating catatonia in a wide variety of patients as a treatable condition that requires prompt identification. Benzodiazepines and electroconvulsive therapy remain first-line interventions. The new DSM-5 Catatonia NEC purports to improve proper diagnosis and early treatment and to intensify research of this condition.

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28
Personality Disorders

C. Robert Cloninger, M.D., Ph.D. and Dragan M. Svrakic, M.D., Ph.D.

Abstract Personality disorder (PD) is the primary psychiatric illness observed in most patients with psychosocial complaints, particularly young adults. PD is present in one-sixth of people in the general population and more than half of all psychiatric patients. Reliable diagnosis of PD can be made in routine clinical practice by brief assessment of two essential features of a person's character—low self-directedness and low cooperativeness—that indicate reduced ability to work and to get along with other people. Subtypes can be distinguished in terms of configurations of temperament traits measuring a person's emotional drives for immediate gratification. PD is usually a lifelong disorder but can mature (remit) spontaneously or with treatment. The temperament and character components of PD are all moderately heritable. Neurobiological findings about personality explain the benefit of differential pharmacotherapy and psychotherapy for different subtypes of PD. The treatment of PD often begins with a stabilization phase with medications and simple cognitive-behavioral approaches. Even in cases of severe PD, more advanced stages of therapy can lead to radical transformation of a person's perspective on life leading to a healthy and stable state of well-being.

Keywords Personality · Personality disorders · Temperament · Character · Pharmacotherapy · Psychotherapy · Meditation · Contemplation · Self-awareness · Well-being

28.1. Introduction: Why Are Personality Disorders Important?

Personality disorders are a serious scientific, psychiatric, and social problem in modern medical practice and in society (1). Personality disorder (PD) is the primary psychiatric illness observed in most patients with psychosocial complaints, particularly young adults. PD is present in about one-sixth of people in the general population, half of all psychiatric outpatients, and two-thirds of patients with a history of psychiatric hospitalization or suicide attempt. People with personality disorders have poor self-esteem, reduced ability to work and to love, and frequent stress responses that lead them to seek medical treatment. They often are less educated, have marital difficulties, and tend to be unemployed. Many cases of substance abuse and criminal behavior in men and women are associated with underlying personality disorder.

In addition to generating chronic personal suffering and/or substantial social or professional consequences, personality disorders predispose an individual to other mental disorders, including substance abuse, mood and anxiety disorders, eating disorders, somatoform and dissociative disorders, and psychoses. Furthermore, personality disorders or extreme personality traits interfere with treatment outcome in psychotherapy, pharmacotherapy, or even electroconvulsive therapy of depression and other clinical syndromes.

C.R. Cloninger, M.D., Ph.D. (✉)
Wallace Renard Professor of Psychiatry, Department of Psychiatry, Washington University School of Medicine, St. Louis, MO, USA
e-mail: clon@wustl.edu

D.M. Svrakic, M.D., Ph.D.
Professor, Department of Psychiatry, Washington University School of Medicine, St. Louis, MO, USA
e-mail: svrakicd@wustl.edu

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Consequently, a solid conceptual understanding and classification are critical to deal with these prevalent and chronic disorders with sensitivity and efficiency. Yet current systems for classification of personality disorders have serious practical and theoretical limitations (2). The concept of personality disorders as sharply delineated categories, as described in the current classifications of the American Psychiatric Association and the World Health Organization, is both imprecise and clinically impractical. The categorical criteria for these disorders overlap and many individuals usually meet criteria for more than one diagnosis. In fact the most common personality disorder diagnosis in DSM-IV was the residual category of personality disorder "not otherwise specified," which is used to designate cases that do not fit any one category well. Such findings raised serious questions about the validity and utility of categorical personality diagnoses.

In DSM-5 an effort was made to develop a system that could combine features of both dimensional and categorical features. Research has consistently shown that the boundaries between mental disorders are not sharply defined, and yet DSM persists in delineating many overlapping disorders while warning clinicians not to reify these diagnoses. The justification offered for this questionable scientific decision is that clinicians find categories easier to use than distinguishing configurations of multiple dimensions, probably because they are accustomed to categorical diagnosis but not multidimensional assessment. The unfortunate result for personality disorder in DSM-5 was to offer a compromise that attempted to combine dimensional and categorical features.

The criteria proposed by the DSM-5 working group on personality disorder were not accepted because the APA's Scientific Review Board regarded the scientific evidence as insufficient for the major changes proposed and the APA's Clinical and Public Health Review Board regarded the criteria as too unwieldy for routine clinical use. As a result, the DSM-IV criteria for personality disorders were retained for official use in DSM-5, but the criteria proposed by the working group were listed as "alternative criteria" for research and clinical consideration. Reference to DSM criteria for personality disorders in this chapter indicates the current official criteria, which are the same in DSM-IV and DSM-5. The alternative DSM-5 criteria are also briefly described so that the reader can appreciate the shortcomings of current criteria that the alternative criteria attempt to address, as well as how the alternative criteria are related to the more coherent approach described herein. Fortunately, scientific research allows a coherent and clinically practical approach to the assessment and treatment of personality and its disorders that transcends the limitations of current official classifications in its utility for understanding etiology, development, and treatment (3–5).

28.2. What Is Personality?

People differ markedly from one another in their outlook on life, in the way they interpret their experiences, and in their emotional and behavioral responses to those experiences. These differences in outlook, thoughts, emotions, and actions are what characterize an individual's personality. More generally, personality can be defined as the dynamic organization within the individual of the psychobiological systems that modulate his or her unique adaptations to a changing internal and external environment (6). Each part of this definition is important for a clinician to appreciate. Personality is "dynamic," meaning that it is constantly changing and adapting in response to experience, rather than being a set of fixed traits. Inflexibility of personality is actually an indicator of personality disorder. Personality is regulated by "psychobiological" systems, meaning that personality is influenced by both biological and psychological variables. Consequently treatment of personality disorders requires growth in psychological self-understanding and not just treatment with medications, although these can be helpful adjuncts to therapy (7). These systems involve interactions among many internal processes, so each person's pattern of adjustment is "unique" to them, even though they follow general rules and principles of development as complex adaptive systems (4). Finally, to understand personality and its development we must pay attention to both the "internal" and "external" processes by which an individual interacts with and adapts to their own internal milieu and external situation. For example, when a person is under stress, they are likely to think and feel differently about themselves and other people. On the other hand, when they are calm and encouraged, they may act more maturely and happily. Everyone has personal sensitivities or "rough spots" that surface when they are under stress. Everyone has "good days" and "bad days," and this pattern of variability over time is what characterizes a person's personality.

28.3. What Is a Personality Disorder?

The diagnosis of personality disorder (PD) requires that the patients have a maladaptive pattern of responses to personal and social stress that is stable and enduring since early adulthood, inflexible, and pervasive. These response patterns lead to chronic and pervasive impairments in their ability to work and to cooperate with others. For example, they may have problems with perfectionism or underachievement, and excessive dependency or social detachment. In addition, most patients with PD consistently have low self-esteem and handle stress poorly. The resulting subjective distress often leads them to complain about anxiety, depression, and worries about physical health. Many patients with personality disorders have problems with impulse

control, such as being too impulsive or too rigid. They also have problems in the way they perceive and interpret themselves, other people, and events, such as cognitive deficits in empathy, tendencies to blame others, and tendencies to be suspicious of others' intentions. Lastly, these patients have difficulty in maintaining healthy lifestyle choices about their diet and personal activities, such as drinking, smoking, and exercise. Consequently, personality and its disorders influence both objective and subjective aspects of physical health. In summary, the abnormal outlook on life that is characteristic of personality disorder leads to impairment in emotional regulation, impulse control, human relationships, cognition, and often physical health.

Individuals with PD typically blame other people or external circumstances for their own physical, psychological, or social problems. Their externalizing of responsibility is a result of two characteristics of PDs to which all clinicians must be alert. First, these patients provoke strong emotional reactions from others but do not recognize the abnormality of their own attitudes, thoughts, and feelings (that is, their symptoms are "ego-syntonic"). Second, they try to change others, instead of changing themselves (that is, their attitude is thus described as "alloplastic"). Both these features reflect an effort to reduce their distress and improve their perceived quality of life.

The diagnosis of PD can be made accurately with little time or expense once their essential features are learned so that they can be recognized and understood.

28.3.1. Clinical Features of Personality Disorders

Current descriptive criteria that are diagnostic of a PD according to the American Psychiatric Association are summarized in Table 28.1.

As shown in Table 28.1, the maladaptive behavior patterns must be "stable and enduring," that is, very long term if not lifelong characteristics. The DSM criteria require that the maladaptive pattern be "of long duration and its onset can be traced back at least to adolescence or early adulthood." In practice it can be difficult to distinguish long-term maladaptation typical of PD and chronic personality changes caused by other mental disorders (such as chronic depression) or long-term situational factors (such as financial dependency on one's spouse). Second, the maladaptive pattern must be inflexible and pervasive, that is, manifest in a wide range of personal and social contexts (i.e., at home, at work, with family, and friends), not only in isolated aspects of the person's life. Finally, there must be substantial evidence of subjective distress, impaired social and occupational function, or both. Subjective distress refers to low self-esteem and limited problem-solving skills, which often lead to anxiety, depression, and somatic complaints. The social and occupational impairments in people with PD result from their immature perspective on life, which is manifest as deficits in self-awareness and character development. More simply, individuals with personality disorders lack mature goals and values.

In addition to these consistent features of all PDs, there is much variation in specific styles of thinking, feeling, and relating. The Diagnostic and Statistical Manual of Mental Disorders (DSM), published by the American Psychiatric Association, distinguishes three clusters of PD (odd, dramatic, and anxious), but features of more than one cluster frequently occur in the same patient. Furthermore, each cluster is subdivided into discrete subtypes of PD (see Table 28.2), but most patients with PD have features of more than one subtype (e.g., narcissistic, histrionic, and antisocial symptoms usually occur together).

In summary, categorical classification systems, including DSM-IV, have failed to help clinicians to deal with PD efficiently. They do provide a quick and rough way to describe the wide range of problems that are characteristic of personality disorder. For example, categorical models convey vivid, clinically descriptive information about the rarely occurring prototypical cases—that is, about those infrequent cases that can be easily "pigeon-holed" in the classification. However, categorical systems do not establish a clear prescriptive relationship between diagnosis and treatment, not even in the rare prototypical cases. In most other medical and psychiatric fields, clinical diagnosis directly indicates optimal treatment. In the field of PD, however, this fundamental goal has not been achieved. The DSM categorical system usually yields multiple personality diagnoses for

TABLE 28.1. Qualitative description of personality disorders.

Discriminating features
A maladaptive pattern of responses to personal and social stress that is
Stable and enduring since teens
Inflexible and pervasive
Causing subjective distress and/or impaired work and/or social relations
Consistent features
Strong emotional reactions elicited from others (like anger or urge to rescue)
Efforts to blame and change others, rather than oneself
Variable features
Odd, eccentric
Erratic, impulsive
Anxious, fearful

TABLE 28.2. Qualitative clusters and subtypes of personality disorders according to the current official criteria of the American Psychiatric Association (DSM-IV, 1994 and DSM-5, 2013).

Cluster	Subtype	Discriminating features
Odd/eccentric		
	Schizoid	Socially indifferent
	Paranoid	Suspicious
	Schizotypal	Eccentric
Erratic/impulsive		
	Antisocial	Disagreeable
	Borderline	Unstable
	Histrionic	Attention-seeking
	Narcissistic	Self-centered
Anxious/fearful		
	Avoidant	Inhibited
	Dependent	Submissive
	Obsessive	Perfectionistic
Not otherwise specified		
	Passive	–
	Aggressive	Negativistic
	Depressive	Pessimistic

individual patients. In such cases, treatment priorities are easily confused. Whether the diagnosis is clear or confused, the clinically most prominent symptoms are likely to be treated most vigorously. However, the most prominent clinical symptoms are often not the most urgent ones to treat. For example, narcissistic persons are likely to be treated for their self-centered behaviors, even though it is their chronically fragile self-esteem that generates most of the narcissistic symptoms.

Furthermore, current DSM-5 categories of PD are symptomatically similar to some major clinical disorders (e.g., paranoid personality and delusional disorder, schizotypal personality and schizophrenia, avoidant personality and social phobia). In fact, most personality syndromes are treated with interventions proven effective for the corresponding major clinical disorders (e.g., antipsychotics for schizotypal PD). Such symptomatic treatments are generally inferior to those derived from the understanding of the underlying causative mechanisms.

Detailed checklists of diagnostic features are available for each of the PD subtypes listed in Table 28.2. Reliable structured interviews are available to make such diagnoses, but the interviews take 90 min or more to complete and, as noted above, usually produce multiple diagnoses (6). Consequently, other approaches are needed in practical clinical work (8).

In contrast to the current official criteria for diagnosis of personality disorders in DSM-IV and DSM-5, DSM-5 also allows consideration of alternative criteria for assessment of personality functioning and pathological personality traits. The alternative assessment is comprised of three components that were developed separately and are not really coherently related to one another. The three components of the alternative assessment approach are a reduced list of specific categories, a description of healthy personality, and a list of five pathological traits like those derived by factor analysis (9).

The alternative criteria for personality disorders in DSM-5 only consider the diagnosis of a reduced set of categories: antisocial, avoidant, borderline, narcissistic, obsessive-compulsive, and schizotypal personality disorders, even though there is extensive scientific support for other disorders, such as histrionic personality disorder. Any system of profiles emerging from 3 to 7 underlying dimensions would require recognition of other syndromes, as illustrated in Figure 28.1. However, the categories in the alternative DSM-5 approach were not systematically derived from the set of five pathological traits delineated in DSM-5, as is done in the psychobiological model of personality. Likewise, healthy personality functioning did not represent the healthy poles of the pathological personality traits. In fact, the description of healthy personality included descriptors closely related to Self-directedness and Cooperativeness. Self-directedness is not the healthy pole of Negative Affectivity because Negative Affectivity includes low Self-directedness combined with high Harm Avoidance.

As a result of these limitations and internal inconsistencies, the alternative criteria provide an approach to diagnosis that was judged by the APA to be inadequately supported by scientific data and too unwieldy for clinical practice.

28.4. Deconstructing the Components of Personality and Its Disorders

Qualitative terms like “inflexible” and “enduring” require subjective judgments and produce little precision in the diagnosis of PD in general. Fortunately, quantifiable components of personality have been identified that allow the differential diagnosis of personality disorders (3, 5, 10). The features that distinguish people with any PD from those with no PD are called character traits.

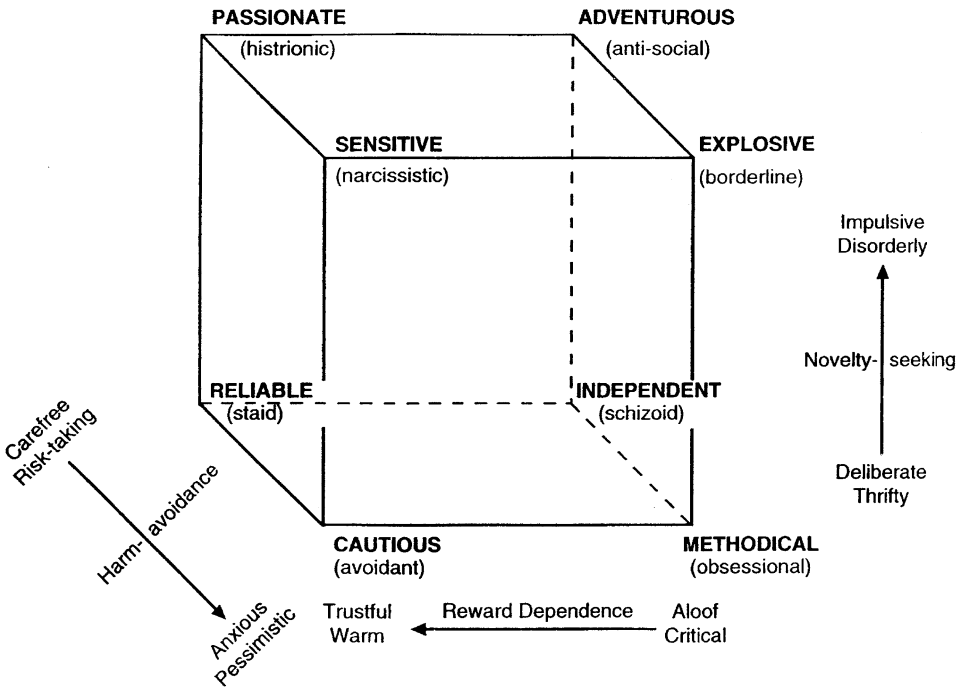

FIGURE 28.1. Discriminating features of most personality disorders shown as the extremes of a cube, with three dimensions defined by novelty seeking, harm avoidance, and reward dependence.

The features that differentiate among subtypes of PD are called temperament traits. More generally, temperament is defined as the emotional core of personality. Character is defined in terms of a person's goals, values, and human relationships. A person's character is based on their outlook on life, which allows them to regulate conflicts among the temperament dimensions. The regulation of emotional drives allows a person to accomplish meaningful goals and to maintain human relationships in accordance with his or her values and needs. Hence, the harmonious integration of personality depends on the coherence of character, not on the temperament configuration.

Three dimensions of character have been distinguished: self-directedness, cooperativeness, and self-transcendence. Self-directed people are responsible, purposeful, resourceful, self-accepting, and dutiful, whereas others are blaming, aimless, helpless, vain, and insecure. Cooperative people are tolerant, empathic, helpful, compassionate, and principled, whereas uncooperative people are prejudiced, uncaring, selfish, revengeful, and opportunistic. Self-transcendent people are intuitive, idealistic, contemplative, faithful, and spiritual, whereas others are self-conscious, pragmatic, judgmental, cynical, and skeptical. Each of these aspects of character are crucial for healthy adaptation to life under current world conditions in which egocentric behavior is threatened to produce mass extinction (5).

It has been repeatedly demonstrated that poorly developed character traits, especially self-directedness, increase the risk for PD substantially. Indeed, most individuals with PD have difficulty accepting responsibility, setting long-term goals, accepting their own limitations, and/or overcoming obstacles they encounter in life. Usually, but not always, they are also uncooperative, i.e., they tend to be intolerant of others, insensitive to other people's feelings, selfish, have difficulty trusting and confiding in other people, and are often hostile and revengeful when others disappoint them, but are quick to take advantage of others in an unprincipled manner when the opportunity arises.

High self-directedness is not always protective against PD. Some narcissistic and antisocial persons may be highly self-directed, i.e., quite resourceful and purposeful and thus successful in pursuing their narcissistic or antisocial goals. Their very low cooperativeness (e.g., intolerance of others, low empathy) and low self-transcendence (e.g., lack of generosity and other virtues) may so interfere with social relations that they have a PD.

While low character traits represent the core features determining the presence or absence of PD, other quantifiable traits are used for differential diagnosis of the DSM clusters (eccentric, dramatic, anxious) and discrete subtypes of PD. The different clusters of PD are distinguished by differences in basic emotions regulated by the temperament dimensions. Four dimensions of temperament have been identified, and are labeled novelty seeking, harm avoidance, reward dependence, and persistence. Individuals high in novelty seeking are impulsive, quick-tempered, extravagant, and dislike rules, as is characteristic of antisocial, histrionic, and other erratic PDs. Individuals high in harm avoidance are anxious, fearful, shy, and fatigable, as is characteristic of avoidant and other anxious PDs. Individuals low in reward dependence are socially indifferent, aloof, cold, and

independent, as is characteristic of schizoid and other odd PDs. Individuals who are high in persistence, such as some mature and some obsessional patients, are industrious and persevering, whereas those who are low in persistence are easily discouraged. Factor analyses have repeatedly supported the validity of the above three DSM clusters of PD (i.e., eccentric/odd, anxious/fearful, erratic/dramatic) except that symptoms for compulsive PD tend to load separately from other PDs, thus forming a fourth cluster (11). The fourth temperament dimension, Persistence, has been shown to correlate with symptoms for obsessive compulsive PD.

Temperament traits regulate the primary emotions of fear (harm avoidance), anger (novelty seeking), and attachment/disgust (reward dependence). Often people with PD impress others as irrational and/or excessively emotional because their behavior and interactions are dominated by extreme temperament traits that are only weakly modulated by character traits. These patients have a rather limited spectrum of the three elementary emotions to respond to everything going on inside and around them. In contrast, mature people have a more complex emotional life including a broad spectrum of so-called secondary emotions, such as humility, compassion, empathy, equanimity, and patience. The likelihood of a well-adapted temperament and mature character is high when these complex emotions are prominent.

Furthermore, different personality subtypes can each be distinguished by a unique combination of values on the temperament dimensions. These can all be assessed by mental status examination or by psychometric testing, as described elsewhere for the interested (http://psychobiology.wustl.edu). For example, borderline PD is characterized by high novelty seeking, high harm avoidance, and low reward dependence. Antisocial personality has the same temperament profile except that harm avoidance is low. It is easy to remember the discriminating features of most personality disorders as the extremes of a cube with three dimensions defined by novelty seeking, harm avoidance, and reward dependence (see Fig. 28.1).

28.5. Stages in the Development of Self-Awareness and Well-Being

A full assessment of personality requires consideration of a person's level of self-awareness and well-being, not just their impairments. Health and well-being are more than the absence of deviant traits. Well-being depends on a person's level of self-awareness and leads to the expression of human virtues and positive emotions that go beyond what is average in contemporary society (4).

There are three major stages of self-awareness along the path to well-being, as summarized in Table 28.3, based on extensive work by many people (4). The absence of self-awareness occurs in severe personality disorders and psychoses in which there is little or no insightful awareness of the preverbal outlook or beliefs and interpretations that automatically lead to emotional drives and actions. Lacking self-awareness, people act on their immediate likes and dislikes, which is usually described as an immature or "child-like" ego state.

The first stage of self-awareness is typical of most adults most of the time. Ordinary adult cognition involves a capacity to delay gratification in order to attain personal goals, but remains egocentric and defensive. Ordinary adult cognition is associated with frequent distress when attachments and desires are frustrated. Hence, the average person can function well under good conditions, but may frequently experience problems under stress. At this stage of self-awareness, a person is able to make a choice to relax and let go of their negative emotions, thereby setting the stage for acceptance of reality and movement to higher stages of coherent understanding.

The second stage of self-aware consciousness is typical of adults when they operate like a "good parent." Good parents are allocentric in perspective—that is, they are "other-centered" and capable of calmly considering the perspective and needs of their children and other people in a balanced way that leads to satisfaction and harmony. This state is experienced when a person is able to observe his or her own subconscious thoughts and consider the thought processes of others in a similar way to observing his or her own thoughts. Hence, the second stage is described as "meta-cognitive" awareness, mindfulness, or "mentalizing."

TABLE 28.3. Three stages of self-awareness on the path to well-being [adapted from Cloninger (4)].

Stage	Description	Psychological characteristics
0	Unaware	Immature, seeking immediate gratification ("child-like" ego-state)
1	Average adult cognition	Purposeful but egocentric Able to delay gratification, but has frequent negative emotions (anxiety, anger, disgust) ("adult" ego-state)
2	Meta-cognition	Mature and allocentric Aware of own subconscious thinking Calm and patient So able to supervise conflicts and relationships ("parental" ego-state, "mindfulness")
3	Contemplation	Effortless calm, impartial awareness Wise, creative, and loving Able to access what was previously unconscious As needed without effort or distress ("state of well-being," "soulfulness")

The ability of the mind to observe itself allows for more flexibility in action by reducing dichotomous thinking (12). At this stage, a person is able to observe himself and others for understanding, without judging or blaming. However, in a mindful state people still experience the emotions that emerge from a dualistic perspective, so mindfulness is only moderately effective in improving well-being (4).

The third stage of self-awareness is called contemplation because it is direct perception of one's outlook—that is, the preverbal assumptions and schemas that direct one's attention and provide the frame that organize and bias our expectations, attitudes, and interpretation of events. Direct awareness of our outlook allows the enlarging of consciousness by accessing previously unconscious material, thereby letting go of wishful thinking, prejudicial biases, and the impartial questioning of basic assumptions and core beliefs about life, such as "I am helpless," "I am unlovable," or "faith is an illusion." For example, many modern psychiatrists are skeptical materialists who are not aware that their reductionistic outlook is an extreme metaphysical assumption for which they have no test or adequate evidence, but which leads them to ignore considerations that are essential for well-being in themselves and their patients (3, 13). In the third stage of self-awareness people begin to become aware of such assumptions and biases of which they had previously been unconscious. The third stage of self-awareness can be described as "soulful" contemplation because in this state a person becomes aware of deep pre-verbal feelings that emerge spontaneously from a unitive perspective, such as hope, compassion, and reverence (4). Contemplation is much more powerful in transforming personality than is mindfulness, which often fails to transform a person's unconscious outlook on life or to reduce feelings of hopelessness (14).

Extensive empirical work has shown that movement through these stages of development can be described and quantified in terms of steps in character development or psychosocial development, as in the work of Vaillant on Erikson's stages of ego development (15). Such development can be visualized as a spiral of expanding height, width, and depth as a person matures or increases in coherence of personality. Likewise, the movement of thought from week to week or month to month has the same spiral form regardless of the time scale. Such "self-similarity" in form regardless of time scale is a property characteristic of complex adaptive systems, which are typical of psychosocial processes in general (4). The clinical utility of this property is that therapists can teach people to exercise their capacity for self-awareness, moving through each of the stages of awareness just described. Their ability to do so, and the difficulties they have, reveals the way they are able to face challenges in life over longer periods of time. Cloninger has developed an exercise, called the "Silence of the Mind" meditation, with explicit instructions to take people thorough each of the stages of awareness as well as they can (4) (see pages 84–95). The first phase of this meditation results in a relaxed state in the first stage of self-awareness. The second phase facilitates entry into the second stage of self-awareness, and the third phase into the third stage of self-awareness, if the person is able to do so. Using this and a way of observing thought during mental status examination, mental health professionals can assess a person's thought and its level of coherence in a way that is constructive, easy, and precise without being judgmental (16, 17).

28.6. Pathophysiology

PD can be understood in terms of the dynamic interactions among the components of a complex adaptive system. Temperament dimensions are inherited biases in adaptive responses to environmental stimuli. The biased adaptive response patterns, in turn, constrain the way character matures—that is, modify the way we view ourselves, others, and the world at large. Character, in turn, has its own unique heritable traits and also modulates the interactions among the temperaments and allows a more-or-less coherent organization of these drives toward meaningful and valued goals. Some illustrative examples of the pathophysiology of some temperament and character traits are briefly described and provided as a foundation for a psychobiological approach to treatment of personality disorders.

The four temperaments influence differences between individuals in their responses to associative conditioning. For example, harm avoidance levels predict the formation of conditioned signals of punishment, but not reward. In other words, individuals high in harm avoidance are more prone to worry because they acquire warning signals about danger more readily than others. Functional brain imaging shows that individual differences in harm avoidance account for about a third of the variance in functional connectivity between the subgenual cingulate region and the amygdala, thereby providing modulation of individual differences in stress reactivity (18). Individual differences in harm avoidance are correlated with low activity in genes that promote expression of the serotonin transporter and the catabolism of dopamine. For example, the genetic vulnerability to depression is expressed when individuals with low activity of the serotonin transporter promoter are exposed to stressful life events. Likewise low activity of tryptophan hydroxylase 2, the rate-limiting enzyme in the synthesis of serotonin, is associated with high harm avoidance in multiple independent studies (19), so serotonergic antidepressants are useful in the treatment of personality disorders with high harm avoidance.

Likewise, reward dependence levels predict the formation of conditioned signals of reward, but not punishment. In other words, individuals high in reward dependence are more sensitive in the exchange of signs of appreciation and approval. High reward dependence levels predict high morning cortisol levels in major depression and also antidepressant responses to serotonergic drugs like clomipramine and nefazodone.

Novelty seeking levels predict quick reaction times and sensitivity to incentive activation of behavior by novelty and conditioned signals of reward. Novelty seeking is modulated by dopaminergic mechanisms; high novelty seeking depends on increased excitability of prefrontal neurons from low postsynaptic sensitivity to dopamine, which inhibits neuronal firing. The gene locus encoding the Dopamine D4 receptor contributes to individual differences in novelty seeking levels in interaction with other genetic and environmental factors that affect dopamine catabolism and reuptake. For example, novelty seeking is increased when individuals with susceptible DRD4 genotypes are reared in a hostile childhood environment.

Given these individual differences in temperament, it is possible to predict the probability and course of character development. For example, PD or immaturity as measured by low self-directedness and cooperativeness is most likely when the temperament profile combines high harm avoidance, low reward dependence, and high novelty seeking. Mature character is most likely when the temperament profile combines low novelty seeking, low harm avoidance, but high reward dependence. The remission of PD involves growth in self-awareness, which depends on complex interactions among many biological, psychological, and social variables. Individuals who are highly self-directed have greater activation of their medial prefrontal cortex, the same area that is activated when individuals become self-aware of what is pleasant or unpleasant to them (4). Likewise, individuals who are highly self-transcendent have greater preservation of their temporoparietal grey matter after middle age than those who are less transcendent. These findings suggest mechanisms by which mental exercises that promote growth in self-awareness also promote the development of maturity and integration of personality.

28.7. Treatment

28.7.1. General Principles

Individuals with PD do not recognize that they are ill and seldom seek help unless other people (such as a spouse, a colleague, or parents) are insistent. This usually happens when maladaptive behaviors create severe marital, family, and/or career problems. In addition, individuals with PD seek help when other associated mental symptoms (e.g., anxiety, depression, substance abuse), or somatic symptoms that frequently complicate PD (e.g., obesity), exacerbate the clinical picture of PD. In general, patients with PD require a multifaceted treatment plan that always combines psychotherapy and pharmacotherapy.

There are three major barriers to effective treatment of PD, but, fortunately, all are preventable errors within the control of the healthcare professional. The first is the frequent loss of professional objectivity, signaled by the development of strong emotions (positive or negative) also called positive or negative counter-transference. Such inappropriate personal involvement is a red flag to reassess the treatment strategy, seek objective supervision of therapy sessions, and, if persistent, mandate referral to another psychiatrist or therapist. Frequent discussions and counseling with colleagues are useful because even strong counter-transference feelings can persist unrecognized.

The second preventable error in PD management is to believe the myth that PDs cannot be treated effectively. This myth is partly initiated by negative counter-transference of some professionals, and then sustained by a failure to consider signs showing the effectiveness of treatment. In other words, belief in the untreatability of a patient sets the stage for a self-fulfilling prophecy. However, many controlled studies indicate that even severe PDs, such as borderline or antisocial, can be effectively treated within an appropriate setting, such as a cooperative therapeutic alliance (20).

The third preventable error in PD management is to give direct advice on personal and social problems. This is counterproductive in patients with PD because they usually become dependent, noncompliant, or resentful. Occasionally, direct advice may be offered to some antisocial, narcissistic, and schizoid patients who are at low risk of developing dependency and need precise structure and direction initially. When tempted to give direct advice to patients, remember that change in personality requires more than common sense and logic. If the relationship leads to frequent advice giving, then referral to a psychiatrist or psychologist may be indicated. People change if they become self-aware and thus able to self-observe, eventually leading to recognition of their own role in chronic dissatisfaction with themselves and their relationships. Personal growth thus arises from new insights about oneself and the environment. Direct advice robs the patient of the opportunity to develop new insights and to learn from his or her mistakes. Although supportive psychotherapy is not recommended with PD patients, supporting their existing coping mechanisms that are mature and adaptive is always useful (e.g., joint evaluation of options and encouragement to practice skills in solving problems).

Substantial personality change, which is invariably needed in people with PDs, involves an extensive reorganization of internalized concepts and coping mechanisms and thus requires precise diagnostic analysis, specific treatment strategies, and expert training. The expert treatment may include any of the several available psychotherapy approaches and is usually combined with pharmacotherapy. The major points relevant to psychotherapy and pharmacotherapy of PDs are summarized below.

As already mentioned, individuals with PD have a peculiar capacity to elicit strong emotions from other people. They are often described as aggravating, unlikable, difficult, or bad. Alternatively, they may be seductive or dependent, and elicit inappropriate emotions or actions, such as sexual interest or the urge to rescue. Even professionals may have difficulty treating them with

respectful objectivity because of a blurring of personal boundaries. Such loss of objectivity occurs because the patient's deeply felt assumptions about other people may often elicit interpersonal responses that are appropriate to the patient's assumptions. Our assumptions about ourselves and others often become self-fulfilling prophecies because of automatic mechanisms of affect transfer. If someone smiles at you, communicating appreciation, it is natural to experience feelings of social attachment and to smile back automatically. Likewise, if someone frowns, communicating anger, it is natural to feel defensive in preparation for his or her angry attack. For example, many patients with PD are suspicious and hostile about others' motives. This distrustful attitude is communicated in many verbal and nonverbal ways and often elicits disagreement or frank hostility from others. These uncooperative responses reinforce the original negative assumptions of the patient, which in turn leads to further alienation.

This vicious cycle of affect transfer can only be interrupted by professional objectivity combined with patience and compassionate respect for the patient's disability. Such objectivity arises from recognizing the overall meaning and implications of their pattern of interpersonal signals, so that their verbal and nonverbal communication takes on diagnostic and therapeutic, rather than personal, significance. In optimal therapeutic relationships, "patients" should be patiently hopeful and physicians should be compassionately realistic. Whenever professionals become aware of strong positive or negative emotions toward a patient (so-called "counter-transference" reactions), this should help to alert them of the possibility that the patient has a PD.

As many patients with PD do not recognize or admit their psychopathology they resist and resent psychiatric diagnoses and any form of mental health treatment. Accordingly, it is prudent to let the patient define his/her treatment goals and then jointly evaluate the likelihood of successful outcome until treatment goals that both patient and therapist agree upon can be identified. Initially, these goals should be as simple and concrete as possible (e.g., "to develop social skills," or "to reduce alcohol use"). In many, but not all cases, successful completion of this initial phase will motivate the patient to define other, more complex treatment goals and to continue treatment.

A psychiatrist should keep in mind that there is a natural succession of stages in the treatment of patients with personality disorders. Each has different goals and requires different methods. The complete psychiatrist should be prepared to guide the patient along these stages, ever ready to advance to the next stage if the patient is interested and prepared to do so.

28.7.2. Four Major Stages in Treatment of Personality Disorders

The four stages in the treatment of a patient with personality disorder can be described as 1) crisis management and stabilization, 2) awakening of a positive perspective and spiritual values in life, 3) illumination, and 4) integrated intelligence (21). The initial stage of crisis management and stabilization deals with the presenting problem and stressors in order to help the patient get into a calm enough state and a working alliance with the psychiatrist. The second stage involves elevating a person's outlook on life so that they can experience things they enjoy and value under relaxed conditions. This involves a spiritual awakening that has often been neglected in strictly cognitive-behavioral or psychodynamic approaches but without which there is little capacity for fundamental change in the quality of life. The third stage of illumination involves increases in self-awareness and capacity for contemplation that elevate a person's usual thoughts, feelings, and relationships in a wide range of conditions. The fourth stage of integration of reason and love in action allows a person to be mature and happy even under conditions that were previously stressful. Patients with PDs can pass through these stages on their own (i.e., remit spontaneously) or be guided through these stages in treatment facilitated by a scientifically designed set of physical, personal, social, cognitive, and spiritual exercises (21).

28.7.2.1. Stabilization Phase

What is done in the first stage of treatment depends greatly on individual patient and his or her presenting situation. This initial stage may involve stabilization of the patient with medications if they are indicated and the patient is interested in such treatment. Medications are often helpful, but not everyone wants such treatment because they always carry some risk of side effects. The advantages and disadvantages must be carefully weighed to respect the patient's wishes and to help them be calm and organized enough for further growth in self-awareness.

A useful approach to the initial stage of treatment is to focus primarily on the chief complaints that bring them to treatment. These complaints are often related to a person's work, relationships, and/or general health, which often offer an adequate basis for the diagnosis and initial treatment of PD. For example, a systematic focus on a person's work, school performance, or relationships can identify attitudes, feelings, and behaviors that help them recognize the barriers to their success and happiness. However, this can bring up many sensitive issues that they prefer to minimize or ignore or that lead them to lie and distort their real situation. An alternative initial approach, particularly if they are entering treatment at the request or demand of someone else, is to focus on healthy lifestyle choices, which provides a non-threatening basis for evaluation of a patient's goals, values, habits, and skills (that is, their personality). Choices about diet, weight control, exercise, smoking, drinking, and ways of relaxing and managing stress are appropriate for discussion with one's physician and do not threaten or stigmatize the patient. Discussion of these choices with a patient can provide a guiding stimulus for developing more self-direction and constructive

planning about life. Discipline in working towards chosen goals is an indicator of maturity. Lack of success stimulates learning about goal-setting and personal growth by, for example, breaking a problem into smaller steps to be taken one at a time. In this process, patients have the opportunity to learn from experience, which is essential for patients with PDs. In many cases, such goal-setting and problem-solving leads to the ability to admit faults and to recognize one's strengths and limitations. Respect for one's self from accomplishment requires acceptance of responsibility and leads to trust of others. Self-respect and respect for others usually progress hand in hand. Such patient guidance is a simplified and non-threatening form of what is usually called cognitive-behavioral therapy and can be safely practiced in a busy office practice with short but regular sessions.

28.7.2.2. Choice of Medications for Stabilization

During the initial stage of treating patients with PDs, medications are often used to target specific symptoms with the goal of relieving subjective distress and/or conflict with others, thereby preparing them for later stages of treatment that require calmness and non-defensiveness to facilitate growth in self-awareness.

The symptomatic pharmacotherapy of persons with PD focuses on the following four groups of symptoms: 1) mood and anxiety dysregulation, related most strongly to Harm Avoidance, 2) aggression and impulse control, related most strongly to Novelty Seeking, 3) social and emotional detachment, related most strongly to Reward Dependence, and 4) psychotic symptoms and cognitive distortions, related most strongly to intellectual reasoning and persistence. Recommendations about drugs of choice in treating PDs are summarized in Table 28.4.

28.7.2.2.1. Anxiety and Mood Dysregulation

Mood dysregulation includes chronic anxiety, emotional lability, and a number of symptoms classified as atypical depression and/or dysphoria (dysphoria and dysthymia are used here as synonymous terms—Latin and Greek for low mood).

TABLE 28.4. Choice of drugs according to target symptoms of personality disorders (used with permission of the Center for Well-Being at Washington University).

Target symptom domains	Drug of choice	Not recommended
I. Behavior dyscontrol (aggression/impulsivity)		
Affective aggression ("hot temper" with normal EEG)	Lithium, SSRIs, anticonvulsants Low dose atypical neuroleptics	? Benzodiazepines
Predatory aggression (hostility/cruelty)	Neuroleptics (atypical) Anticonvulsants, beta-blockers	Benzodiazepines
Organic-like aggression (disinhibition)	TCAs (imipramine) Low dose, weak anticholinergic atypicals Anticonvulsants Cholinergic agonists (donepezil)	Benzodiazepines
Ictal aggression (abnormal EEG)	Carbamazepine, valproates Diphenylhydantoin Benzodiazepines (clonazepam)	
II. Mood dysregulation and III. Anxiety		
Emotional lability	Lithium, lamotrigine, valproates Low dose atypicals (olanzapine, clozapine)	TCAs
Depression Atypical depression/dysphoria	MAOIs, SSRIs Atypical neuroleptics (clozapine, aripiprazole, quetiapine)	
Major depression (typical)	TCAs (males), SSRI (females)	
Emotional detachment	Atypical neuroleptics (clozapine, aripiprazole, quetiapine)	? TCAs
Chronic cognitive anxiety	SSRI, MAOIs Benzodiazepines	
Chronic somatic anxiety	MAOIs, SNRIs (duloxetine, milnacipran) Beta blockers, GABA analogs (topiramate) TCAs (amitriptyline, imipramine)	Benzodiazepines (risk of abuse)
Acute and severe anxiety	Low dose neuroleptics (atypicals, e.g., quetiapine)	
IV. Cognitive distortions/psychotic symptoms		
Acute and brief psychotic episodes	Atypical neuroleptics Low-dose typical neuroleptics	
Chronic low-grade psychotic like symptoms	Atypical neuroleptics Low-dose typical neuroleptics	

Patients with PD often present with chronic cognitive anxiety (anticipatory worry) and/or chronic somatic anxiety (concerns about bodily pains and psychophysiological reactions). Cognitive anxiety is most responsive to benzodiazepines and GABA analogs (e.g., valproates, gabapentin), whereas somatic anxiety is more responsive to Monoamine Oxidase Inhibitors (MAOIs), Selective Serotonin Reuptake Inhibitors (SSRIs—such as fluoxetine, paroxetine, fluvoxamine), Serotonin Norepinephrine Reuptake Inhibitors (SNRIs—such as venlavaxine or duloxetine), and buspirone. Low doses of tricyclic antidepressants are very effective for somatic anxiety in some patients, but MAOIs are more often effective if the required dietary regimen can be followed or patch systems (transdermal selegiline) are used. Avoidant traits can be also effectively treated with either SSRIs or MAOIs. Some components of somatic anxiety, such as sweating, palpitations, diarrhea, and tremor, can be treated with beta blockers. Severe, psychotic-like anxiety responds to low dose neuroleptics, especially drugs with relatively weak D2 antagonism (e.g., quetiapine) or partial D2 agonism (e.g., aripiprazole). Despite relative safety of novel atypical drugs caution about prolonged use is necessary.

Emotional instability (manifested as severe and frequent mood swings) is usually responsive to lithium (for those with frequent episodes of euphoria) or lamotrigine or valproate (for those with more frequent depressive episodes) or with both (for patients with both euphoric and depressive episodes). TCAs like imipramine, sometimes increase impulsivity and anger in emotionally unstable patients (e.g., borderline, narcissistic, histrionic, dependent). TCAs are extremely dangerous in an overdose, so these drugs ought to be used with caution in patients with PD.

Atypical depression and dysphoria, frequent in PD, are rarely responsive to TCAs. In fact, at least half of the PD subjects suffering from atypical depression worsen on TCAs. Atypical depression does respond well to SSRIs, MAOIs, or possibly neuroleptics (especially promising is the atypical drug aripiprazole). Again, antipsychotics are only used after careful consideration of the risk-benefit ratio. In contrast, classical depressive episodes, which complicate PD, are treated with antidepressants, including heterocyclics, in doses suggested for primary major depression.

28.7.2.2.2. Aggression

It is useful, though sometimes difficult, to distinguish different types of aggression. The most common form occurs when a quick-tempered person is provoked by frustration or threats. This "affective aggression" is frequent in impulsive-aggressive individuals (that is, those high in novelty seeking and low in harm avoidance). Aggression that appears to be unprovoked sometimes occurs in patients with cerebral instability documented by an abnormal EEG, and is often called "ictal aggression" regardless of any associated personality traits. Predatory aggression or "cruelty" involves hostile revengefulness and taking pleasure in victimizing others, often with intact impulse control. Such predatory aggression is most frequent in individuals who are very low in cooperativeness, which is most likely seen in antisocial and borderline PD. Lastly, "organic-like" aggression is often accompanied by poor social judgment and disinhibition. It is best distinguished from other impulsive-aggressive syndromes by prominent distractibility, inattention, and emotional lability, as is characteristic of patients with frontal lobe lesions. Also, such patients often manifest high somatic anxiety with panic and cardiorespiratory symptoms, muscular tension, and motor restlessness.

Multiple double-blind trials have shown efficacy of lithium in the treatment of affective aggression. Lithium salts help impulsive-aggressive individuals to be more reflective, that is to think about consequences before acting on impulse. To a lesser extent, lithium may be helpful in reducing cruelty and lack of cooperativeness, but this may be an indirect result of reducing impulsivity, which often is a predisposing influence in the development of hostility and revengefulness. Likewise, low-dose atypical neuroleptics may be useful in modifying old habits and assist in reducing affective or predatory aggression. The decision to use neuroleptics long-term requires consideration of potential side effects, such as tardive dyskinesia or metabolic dysregulation, and should be made with carefully informed consent of the patient. Anticonvulsants, such as valproate, lamotrigine, carbamazepine, and oxcarbazepine (to mention only those most frequently used), reduce both the intensity and the frequency of unprovoked angry outbursts in many patients regardless of normality of their EEG. Double-blind trials have shown that psychostimulants, such as methylphenidate, are often beneficial in the treatment of inattentive and hyperactive adults who are impulsive and aggressive, especially when the symptoms have begun in early childhood. Antidepressants (particularly SSRI and SNRIs) are considered by many to be beneficial for certain impulsive subtypes of PD (e.g., borderline, histrionic). Finally, monoamine oxidase inhibitors (MAOI) are effective in some dysphoric states with somatic anxiety and hostility.

There are some relative contraindications for these drugs. Lithium should not be given to antisocial persons without aggression and impulsivity because it does not diminish non-aggressive antisocial behaviors (such as cruelty, lying, cheating, and stealing). Likewise, benzodiazepines and alcohol have disinhibiting effects on violence, reduce conditioned avoidance behavior ("loosen inhibitions"), and further impair passive avoidance learning in impulsive antisocial persons.

28.7.2.2.3. Emotional Detachment

Cold and aloof emotions, and disinterest in social relations ("chronic asociality") is typical of schizoid and schizotypal persons, and, to a lesser extent, antisocial, paranoid, and some narcissistic persons. In cases where these symptoms reflect an underlying depression, antidepressants (SSRIs or MAOIs) frequently help. One should be cautious with TCAs in schizotypal PD, for they may

worsen and/or trigger psychosis. In many cases, emotional detachment responds to atypical neuroleptics like aripiprazole, olanzapine, or risperidone, which may reduce social withdrawal and other features of eccentric PDs with less risk of extrapyramidal symptoms than with typical neuroleptics. However, dose adjustment is crucial to maintain compliance because patients with PD often have little tolerance for side effects.

28.7.2.2.4. Psychoses

Acute, brief reactive psychoses may complicate most subtypes of PD. These are treated symptomatically, according to accepted pharmacological practices. In general, PD patients with an episode of psychosis are likely to respond to and comply with either low doses of powerful neuroleptics or atypical neuroleptics. Due to much better safety and tolerability, new antipsychotics are now the first choice for these symptoms. Acute psychotic symptoms requiring medication may subside when environmental stressors are brought under control; thus one should be ready to lower the dose or discontinue the medication.

Some PD patients manifest chronic, low-level psychotic-like symptoms, such as thought disorders (ideas of reference, magical thinking, odd fantasies, suspiciousness), unusual perceptual experiences such as illusions, and odd/ eccentric behaviors. These chronic, low-level, psychotic-like symptoms have been shown to respond to low-dose powerful neuroleptics like haloperidol. There is no data on atypical neuroleptics for these symptoms, although it seems reasonable to expect them to be efficacious. Some chronic cognitive disturbances, such as mild ideas of reference or suspiciousness, tend to subside when the background emotional tension is reduced. For example, alprazolam has been found to be beneficial in patients with borderline personality manifesting ideas of reference or suspiciousness. However, long-term use of benzodiazepines is associated with high risk of drug dependence, particularly in patients with PDs, so benzodiazepines like alprazolam should be prescribed only after careful consideration of the risk-benefit ratio and their use carefully monitored for evidence of abuse or dependence.

28.7.3. Advanced Stages of Personality Transformation

Neither medications nor cognitive-behavioral and psychodynamic approaches, alone or in combination, are usually adequate to transform a person's personality in a fundamental way. Individuals who radically change their perspective on life usually attribute the change to getting a good job that provides a sense of self-respect, marrying a loving and trusted spouse, or experiencing a religious conversion. These kinds of life experiences change a person's initial perspective on life, which in turn transforms their thoughts, feelings, and behavior. Cognitive-behavioral and psychodynamic therapies often leave a patient in a tense inner-struggle with themselves unless treatment provides experiences that allow a reevaluation of basic assumptions about life. Otherwise a person cannot transcend the conflicts among their emotional drives, so he or she remains in constant or recurrent struggles among parts of him or her self.

A systematic approach to personality transformation without tension or conflict is described in more detail elsewhere (4, 21). The second stage of treating PD involves the awakening of the positive outlooks on life that are needed for well-being, as described in Table 28.5. The basic principles of well-being are summarized in Table 28.5 along with therapeutic experiences and activities for patients that are designed to help them value the dignity of their life and that of others as human beings as a

TABLE 28.5. Cultivation of well-being (used with permission of the Center for Well-Being at Washington University).

	Experiences and activities	
Positive approaches to well-being	**Recommended**	**Not recommended**
1. Letting go of struggles	Acts of hope and self-direction	Any violence, fighting
	Accepting responsibility	Complaining or blaming others
	Silence of Mind, phase 1[a] (calm reflection)	Consumerism feeding greed/addiction
2. Working in the service of others	Acts of kindness/cooperation	Divisions feeding fear and hate
	Purposeful giving of oneself	Possessiveness and hoarding
	Union in nature[a]	Seeking power and dominance
	Silence of mind, phase 2[a] (mindful meditation)	
3. Growing in awareness	Acts of faith and humility	Criticism or praise of self and others
	Transcendent problem-solving	Depending on external direction
	Union in nature[a]	Denial of what we don't understand
	Listening to the heart[a]	
	Silence of mind, phase 3[a] (contemplation)	
4. Understanding thought processes	Calm reflection	Seeking justification
	Mindful meditation	Depending on external advice
	Contemplation (silence of mind, all three phases)	Depending on intellect alone

[a]Meditations for coherence therapy with assessment, treatment, and training information are available for interested clinicians (Cloninger (4), http://psychobiology.wustl.edu), and the nonprofit Anthropedia Foundation (see http://anthropedia.org).

TABLE 28.6. Physical, personal, social, cognitive, and spiritual therapeutic procedures for advanced character development (Advanced Stages of Coherence Therapy for Personality Disorders) (used with permission of the Center for Well-Being at Washington University).

Target problems	Character goals	Recommended experiential activities
1. Mood dysregulation (feeling separate, intolerant/hateful, self-critical, catastrophizing/distressed, victimized)	Trust and self-respect	Psychoeducation about health, sex, stress Physical exercise for relaxation and fitness Reconciliation of anxiety versus risk-taking Recognition of immature automatic thoughts Team-work to build trust and respect
2. Aggression/impulsivity (being violent, angry, frustrated, greedy/jealous, proud, selfish)	Impulse control and self-mastery	Psychoeducation about nutrition, biorhythms Self-efficacy about cravings/substance abuse Reconciliation of impulsivity vs rigidity Non-violent assertive communication Social service and acts of forgiveness
3. Social dysregulation (feeling rejected, detached, insecure or cold, unappreciated, unfriendly)	Empathy and secure attachments	Psychoeducation about social signals Empathy training and active listening skills Reconciling approval-seeking vs aloofness Social problem solving Therapeutic touch and appeasement
4. Cognitive distortion (feeling meaningless, judgmental, dualistic, afraid of death, lacking faith)	Mindfulness and meaning	Psychoeducation about self-transcendence Practice of mindfulness meditation Reflection on mysteries and mythology Creative works (art, music, writing, etc.)
5. Emptiness (seeking fulfillment, satisfaction, positive emotions, integrated intelligence, virtue, well-being)	Virtue and well-being	Psychoeducation about well-being Recognizing triggers of negativity Well-being Coaching

Treatment and training materials available through http://anthropedia.org (8, 23).

result of self-awareness of each person's body, mind, and soul. Psychiatry literally means the "healing of the soul" but this important insight has been neglected or denied as a result of the errors of materialistic and reductionistic thinking (4). What is meant here by a spiritual awakening is that the patient becomes directly aware that their worldview (that is, their outlook on life) has an impact on their thoughts, emotions, and actions. Our outlook on life is what makes us vulnerable to mental disorders so we must become aware of the assumptions implicit in our initial perspectives. Without some degree of awareness of the consequences of our initial perspective, it is not possible to transcend the conflicts and contradictions in our thoughts and emotions that derive from these more-or-less coherent outlooks. As a result, psychotherapies that neglect the stage of spiritual awakening inevitably leave their patients locked in an inner struggle among parts of themselves from which there is no escape, as described poignantly by Freud about himself (22). Materials for use in personality assessment, training of therapists, or for such therapy for PD and other mental disorders are available for interested clinicians who wish to mitigate such interminable conflict (http://psychobiology.wustl.edu).

Once there is an awakening of self-awareness to a meta-cognitive level, then a patient can proceed to the advanced stages of treatment that are briefly summarized in Table 28.6. Notice now that the patient is behaviorally stable and self-aware, then it is possible to focus on the causes of the symptoms that were targets of initial intervention during the stabilization phase. For example, the causes of anxiety and dysregulated mood are rooted in a patient's lack of self-respect and trust of others, as expressed in their feelings of separateness, catastrophe, and victimization (see Table 28.6). The therapeutic strategies for addressing each of these sets of causes include psychoeducation, physical and other nonverbal therapies (e.g., psychomotor activities), emotional skills training, cognitive skills training, and spiritual exercises. As a result, no one form of therapy (such as behavioral, cognitive, interpersonal, or psychodynamic) is really comprehensive, even with addition of modules from positive psychology or mindfulness training.

Notice in Tables 28.4 and 28.6 also that the symptomatic targets for psychobiological treatment correspond closely to the skill training modules that have been shown to be moderately effective in the treatment of severe personality disorders (14) except that the focus is shifted from a behavioral approach to the cognitive perspectives or schemas that lead to the behavioral problems. In addition, a non-dualistic approach is taken of a stepwise path of character development to well-being and emphasis is placed on reconciliation of emotional conflicts that can be measured by the extremes of each of temperament dimensions. In essence, the extremes of each temperament are transcended by the development of particular forms of spiritually elevated thoughts—namely, self-respect reconciles the extremes of Harm Avoidance, self-mastery reconciles the extremes of Novelty Seeking, secure attachments reconcile the extremes of Reward Dependence, and virtues and transcendent meaning reconcile the extremes of Persistence and the limits of the finite human intellect. More information about transcendence and sublimation is described elsewhere (4). Both extremes of each temperament have advantages and disadvantages, and transcendence of the underlying conflict resulting from these disadvantages allows a person to live without tension or conflict about these issues as a result of a more holistic initial perspective.

A major practical advantage of therapy modules that focus on the reconciliation of both extremes of each temperament is that heterogeneous groups of patients with widely different personality profiles can be treated together. The focus is on transcending emotional conflicts, coherent character development, and well-being for everyone, not particular personality subtypes. The stigma linked to PD and mental disorders in general is mitigated by facing the facts that everyone is imperfect but can learn to live without fear along the path to well-being. The design of therapies has often failed to recognize the path of development of character and well-being and the crucial role of spirituality in transcending and sublimating emotional conflicts. Psychotherapies have almost entirely focused on thought and have generally ignored the body as well as the soul, as a result of the influence of errors in dualistic, behavioral, materialistic, or psychoanalytical thinking. Such an intellectual stance is arrogant and ultimately self-defeating. Alternative therapies have focused on methods that emphasize the body and ignore the benefits of medications or psychodynamics (23), which is equally arrogant and self-defeating. The coherence therapy described here is based on an integrative psychobiological approach that attends in a balanced way to all three aspects of our being—body, mind, and soul. There is no incompatibility between biological, psychological, or spiritual aspects of the treatment of PD. In fact, there is a crucial synergy between the components of treatment directed at each aspect because our rational brains do not function well when the emotional brain (i.e., limbic system) is distressed. There is much to be learned about the treatment of PD and related mental disorders, but the approach outlined here provides a paradigm that will allow the clinician to integrate what they know about people and bring that to help and guide their treatment of every patient they encounter. It should be emphasized again that advanced psychotherapy or use of psychotropic medications for treatment of PD requires expert training or close supervision by an experienced psychiatrist. This is a rapidly advancing area of psychiatry. Continuing education about the treatment of PD is likely to be especially rewarding for both psychiatrists and their patients because it offers a crucial gateway to the path to well-being and reduced disability from the full range of mental disorders.

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Part IV
Special Areas

29
Genetics of Psychiatric Disorders

John I. Nurnberger Jr., M.D., Ph.D., Wade Berrettini, M.D., Ph.D.,
and Alexander B. Niculescu III, M.D., Ph.D.

Abstract The major psychiatric disorders are common disorders with a complex genetics, similar to other common medical disorders such as diabetes and hypertension. For most of these disorders, linkage studies in families with multiple cases have revealed chromosomal areas that contain susceptibility genes. In recent years, genes have begun to be identified for disorders such as schizophrenia (e.g., DISC1, TCF4, ZNF804A), bipolar affective disorder (CACNA1C, ODZ4), autism (neuroligins, neurexins), attention deficit disorder (DAT, DRD4), and alcohol dependence (GABRA2, ADH4). Genetic studies of Alzheimer's Disease (APOE) and several forms of mental retardation (Down's Syndrome, Fragile X) are already well advanced. Functional studies related to single gene vulnerability factors are now beginning. Important clues are emerging from gene expression studies and epigenetics. It is anticipated that new diagnostic tools and therapeutic strategies will result from this work.

Keywords Genetics • Schizophrenia • Bipolar affective disorder • Candidate genes • Molecular genetics • Alcohol dependence

29.1. Methods in Psychiatric Genetics

A scientific revolution has occurred in the field of genetics with the advent of molecular biological techniques. Using these techniques, genes influencing risk for many neuropsychiatric diseases have been identified: initially Mendelian single gene conditions such as Huntington's disease were resolved; in the last few years complex genetic conditions such as alcohol dependence, autism, bipolar disorder, and schizophrenia have yielded specific genes. Some of this work has been facilitated by the study of endophenotypes, or biologic vulnerability markers.

J.I. Nurnberger Jr., M.D., Ph.D. (✉)
Joyce and Iver Small Professor, Department of Psychiatry, Director, Institute of Psychiatric Research,
Indiana University School of Medicine, Indianapolis, IN, USA
e-mail: jnurnber@iupui.edu

W. Berrettini, M.D., Ph.D.
Professor, Department of Psychiatry, University of Pennsylvania, Director,
Center for Neurobiology and Behavior, Philadelphia, PA, USA
e-mail: wadeb@mail.med.upenn.edu

A.B. Niculescu III, M.D., Ph.D.
Associate Professor, Department of Psychiatry, Institute of Psychiatric Research,
Indiana University School of Medicine, Indianapolis, IN, USA
e-mail: anicules@ipupi.edu

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29.1.1. Clinical Epidemiology: Twin, Family and Adoption Studies

These three types of population genetic studies are conducted to ascertain whether a particular human phenomenon is substantially genetically influenced:

Twin studies are based on the fact that monozygotic (MZ) or identical twins represent a natural experiment in which two individuals have the exact same genes. This is in contrast to dizygotic (DZ) or fraternal twins who share 50% of their genes and are no more genetically similar than any pair of siblings. A phenomenon which is under genetic control should be more "concordant" (similar) in MZ twins compared to DZ twins.

Family studies can answer three critical questions concerning the inheritance of a disorder:

1. Are relatives of an affected subject at increased risk for the disorder compared to relatives of control subjects?
2. What other disorders may share a common genetic vulnerability with the phenomenon in question?
3. Can a specific mode of inheritance be discerned?

A family study typically begins with a proband or initially ascertained patient, whose relatives are then studied. Adoption studies: the risk for the disorder may be evaluated in four groups of relatives: the adoptive and biological relatives of affected adoptees and the adoptive and biological relatives of control adoptees. If the disorder is heritable, one should find an increased risk among the biological relatives of affected subjects, compared to the other three groups of relatives. One can also compare risk for illness in adopted-away children of ill parents versus adopted-away children of well parents.

29.1.2. Segregation Analysis

Segregation analysis is used to determine whether the pattern of illness in families is consistent with a specific mode of transmission. This is most useful for a condition in which a single gene accounts for a substantial portion of the variance. Most major psychiatric disorders, as presently defined, do not fall in this category.

Some of the complexities of major psychiatric disorders include:

1. Variable penetrance (some individuals with the genetic predisposition will not manifest the disease),
2. Phenocopies (individuals without a genetic predisposition who manifest the symptoms of the disease),
3. Genetic heterogeneity (more than one type of genetic cause can produce the same syndrome),
4. Uncertainty regarding the diagnostic boundaries of a syndrome,
5. Pleiotropy (one gene may be expressed in different ways in different persons).

29.1.3. Linkage Analysis

At any given genetic locus, each individual carries two copies (alleles) of the DNA sequence which defines that locus. One of these alleles is inherited from the mother and the other is inherited from the father. If two genetic loci are "close" to each other on a chromosome, their alleles tend to be inherited together (not independently) and they are known as "linked" loci. During meiosis, crossing over (also known as recombination) can occur between homologous chromosomes, thus accounting for the observation that alleles of linked loci are not always inherited together.

The rate at which crossing over occurs between two linked loci is directly proportional to the distance on the chromosome between them. In fact, the genetic distance between two linked loci is defined in terms of the percentage of recombination between the two loci (this value is known as theta). Loci that are "far" apart on a chromosome will have a 1/2 chance of being inherited together and thus are not linked. Thus, the maximum value for theta is 0.5, while the minimum value is 0. Linkage analysis is a method for estimating theta for two or more loci.

The probability that two loci are linked is the probability that theta < 0.5. The probability that the two loci are not linked is the probability that theta $= 0.5$. Thus, a LOD (logarithm of the odds ratio) score for a family or set of families is defined:

LOD score $= \log_{10}$ [probability of theta < 0.5/ probability of theta $= 0.5$]

Although it is possible to perform such calculations by hand (1), LOD scores are usually calculated using computer programs, such as GENEHUNTER or Merlin. Since a LOD score is a log value, scores from different families can be summed. For complex conditions collections of affected sib pairs may be studied rather than large families. A LOD score of 1.0 indicates that linkage is 10 times more likely than non-linkage. For simple genetic conditions, a LOD score of 3 or greater is evidence for linkage, while a score of −2 or less is sufficient to exclude linkage for the sample studied. For disorders with more complex forms of inheritance (including most psychiatric disorders), a higher positive LOD score is required (3.6 for definite linkage and 2.2 for suggestive linkage). See Lander and Kruglyak (2) for further discussion.

29.1.4. Association Studies

In association studies one compares allele frequencies for a given locus in two populations, one of which is composed of unrelated individuals who have a disease (cases), while the "control" population is usually composed of ethnically similar unrelated persons who do not have the disease. If a particular allele commonly predisposes individuals to the disease in question, then that allele should occur more frequently in the case population, compared to the control population.

There are potential pitfalls to an association study. The locus chosen for study should predispose to illness. Thus, loci chosen for association studies are often known as candidate genes. If the locus does not predispose to illness, then the association study should be negative. However, false positive results can occur if the two populations are not carefully matched for ethnic background. One alternative control group is the parents of affected individuals (the nontransmitted alleles are studied—this is known as the Transmission Disequilibrium Test or TDT) (3).

29.1.5. Genome-Wide Association Studies (GWAS)

Genome-wide association studies (GWAS) were introduced in 2006. They were made possible by chip technology in which up to 2.5 million SNPs may be tested within a single experiment. This methodology enables examination of virtually every gene in the genome with multiple SNPs, and, because of linkage disequilibrium (the fact that nearby variants tend to be transmitted together not only within families but also within a population), even detection of variation some distance from the actual SNP tested (4). The major limitation of GWAS studies is interpreting the data, since the number of simultaneous tests is massive, and requires statistical corrections that are complex, and not all events are independent due to linkage disequilibrium (the tendency for nearby alleles to be inherited together in populations). The presently accepted threshold for genomewide significance for a SNP association with illness in a GWAS study is 5×10^{-8} (5), based on the empirical probability of a type I error. Since the effect size of variants associated with psychiatric disorders is generally quite small (odds ratios of 1.1–1.2 are the norm), achieving p values that meet this threshold requires very large sample sizes. Complex traits such as height, and risk for type II diabetes have now been analyzed extensively with GWAS methods, but success required samples in the tens of thousands or even hundreds of thousands (6). These samples are achievable now only by extensive collaboration involving multiple sites, usually from international sources. Each set of cases should be matched with controls from a similar ethnic background because of the extensive variation in SNPs on the basis of ancestry. This ethnic variability is generally assessed formally using multidimensional scaling (MDS) or a similar method.

GWAS methods have now proven to be useful in psychiatric disorders, with several loci meeting stringent criteria in both schizophrenia and bipolar disorder (7, 8). Several of the loci described previously are the product of GWAS investigations (e.g., ANK3, CACNA1C, NCAN).

GWAS datasets have also been used for additional studies that extend the reach of the association methodology: polygenic score analyses and pathway analyses. The polygenic score method was introduced in neuropsychiatric disorders by Shaun Purcell as part of the International Schizophrenia Consortium (9) report on GWAS findings in an initial dataset. The idea is to assign a score to each risk allele that is even nominally associated with disease (using a weighting factor based on the ratio of allele frequency in cases to allele frequency in controls) and then add the scores for each individual based on the number of risk alleles that individual carries. The risk alleles from one population may be tested to see whether they predict illness in a second population. In the ISC paper, risk scores for a group with schizophrenia successfully predicted illness in a second population with schizophrenia, and also in a separate population with bipolar disorder, but not in groups with several other medical conditions. This suggested substantial genetic overlap between the schizophrenia and bipolar disorder samples. Subsequently, Niculescu and colleagues used the ISC data along with gene expression and other lines of evidence, from human and animal models studies, to prioritize the most likely candidate genes for schizophrenia, using a convergent functional genomics approach (10). They were able to show that nominally significant SNPs in a small panel of 42 top prioritized genes were able to distinguish between schizophrenics and controls and predict illness in four independent cohorts of two different ethnicities.

Pathway analyses start with the premise that multiple genes (each one explaining a small portion of the overall genetic variance) are involved in the predisposition for complex neuropsychiatric disorders and that it will be more parsimonious and heuristic to explain their effects in terms of the biological pathways that they participate in rather than considering them individually. SNPs that show evidence for association (even though not meeting the stringent criteria of 5×10^{-8} discussed above) are considered markers for genes that they reside in or are very close to. The gene lists generated in this manner are compared with "canonical pathways" or gene lists designated in bioinformatic databases. Commonly used databases for this purpose include Gene Ontology (GO, www.geneontology.org/) or KEGG (www.genome.jp/kegg/), or the proprietary database Ingenuity (www.ingenuity.com/). Statistical analysis may be conducted at the pathway level, usually correcting for gene size, which varies over several orders of magnitude. Published studies on pathways in bipolar disorder using GWAS information include Torkamani et al. (11), Holmans et al. (12), Pedroso et al. (13), O'Dushlaine et al. (14), Le-Niculescu et al. (15), and the PGC

BP Working Group (16) and several other reports which are in preparation. Our own analysis (17), which includes much of the data in the previous published reports as well as additional data not available at the time, suggests that pathways involved in the genetic predisposition to BP include hormonal regulation, calcium channels, second messenger systems, and glutamate signaling. Gene expression studies implicate neuronal development pathways as well. A recent analysis of GWAS data from 5 major psychiatric disorders (autism, attention deficit hyperactivity disorder, bipolar disorder, major depression, and schizophrenia) identified four loci (including two calcium channel subunit genes, CACNA1C and CACNB2) that appear to be common vulnerability factors to all disorders. Pathway analyses in these data (33 332 cases and 27 888 controls of European ancestry) show a general association with genes related to calcium channel activity and vulnerability to psychiatric disorder (18) (Fig. 29.1).

Investigators just recently acquired a new tool for interpretation of GWAS data. It has been observed that many of the GWAS "hits" for complex disease in general are not in coding regions of genes. Some are in promoter regions, which are known to affect nearby genes. But many are in intergenic regions or intronic (non-coding) regions of genes. Data from the ENCODE project (19) now enable us to define the functions of these gene variants that are found in non-coding regions. By and large they are regulatory variants, most of which work by altering DNA sequence that affects the binding of transcription factors. The transcription factors are proteins that turn on and off specific genes and sets of genes. We now believe that the functions of many of the GWAS variants may be elucidated by knowledge of which transcription factors bind to those genomic areas. As an example, one may use the site HaploReg (http://www.broadinstitute.org/mammals/haploreg/haploreg.php) to determine that many of the BP GWAS hits may work by affecting the binding of the POU family of transcription factors, which in turn regulate genes involved in pituitary development and hormonal expression.

The prevailing scientific opinions of GWAS studies over the past five years are instructive to observe. Initial expectations of the methodology were extremely enthusiastic, since this was the first method to permit whole genome investigation of each of the ~20,000 genes in the human genome. After the first set of studies, there was a bit of a "backlash", not just in relation to psychiatric syndromes but to common diseases in general, as initial findings often did not pass statistical scrutiny. There was wide discussion of the "problem of missing heritability," and concern that the answers must lie in examination of rare variants (those of less than 1% frequency) or even "private" variants (those found in single families). Such rare variants are now being identified, though they do not yet account for a substantial portion of the genetic variance in vulnerability to major psychiatric disorders. More recent statistical analyses show that common variants indexed by GWAS likely account for a substantial portion of the heritability of most common conditions [about 40% of the heritability for bipolar disorder, for instance—Lee et al. (20)], and that therefore it will be very valuable to assemble the large samples of cases necessary to identify those variants specifically and to understand the biologic pathways that they perturb.

29.1.6. Sequencing Studies

Sequencing Studies have been initiated in a number of major psychiatric disorders including bipolar disorder. Sequencing (also referred to as "re-sequencing") now uses "next generation" methods that are many times cheaper and more efficient than the common PCR-based methods in use several years ago. The two strategies generally employed are Whole Genome Sequencing and Exome sequencing, the former involving determination of every base pair in a subject's genome and the latter involving just the ~2% of the genome that is directly transcribed or in known regulatory regions. An important variable in sequencing endeavors is the "read frequency" or the number of times that an area is analyzed for sequence information. Up to 30 reads may be necessary to identify some rare mutations precisely, but 8 reads may be sufficient to identify most variants. The major advantage of sequencing over GWAS is that sequencing is better for identifying rare variants (e.g., less than 1% frequency in cases), some of which are anticipated to have large effects on illness vulnerability.

Analysis of sequence data presents currently unsolved computational problems, since there are 3×10^9 datapoints per person, including several hundred thousand rare variants per person (21), and 250–300 loss of function variants in annotated genes (22). How does one identify the pathogenic variants within these huge datasets? Current studies have relied on lists of genes previously reported to be associated with the disorder in question, as well as strategies of collapsing different variants within single genes or even single regions. We expect that statistical methods will evolve quickly in this area to help answer this question and strengthen the value of sequencing methods for defining the genetics of bipolar, and other, disorders.

29.1.7. Copy Number Variation (CNV)

Studies of copy number variation (CNVs) have been ongoing for several years in neuropsychiatric disorders. CNVs are cytogenetic abnormalities that are too small to resolve using microscopic examination of the chromosomes, but still large enough to involve hundreds or thousands of base pairs. They are, therefore, mini-duplications or deletions of genetic material. They have been found to be widespread in healthy individuals, but have also been reported to be concentrated in areas of possible significance for autism (23), intellectual disability (24), and schizophrenia (25). They may either be *inherited* or *de novo*, and

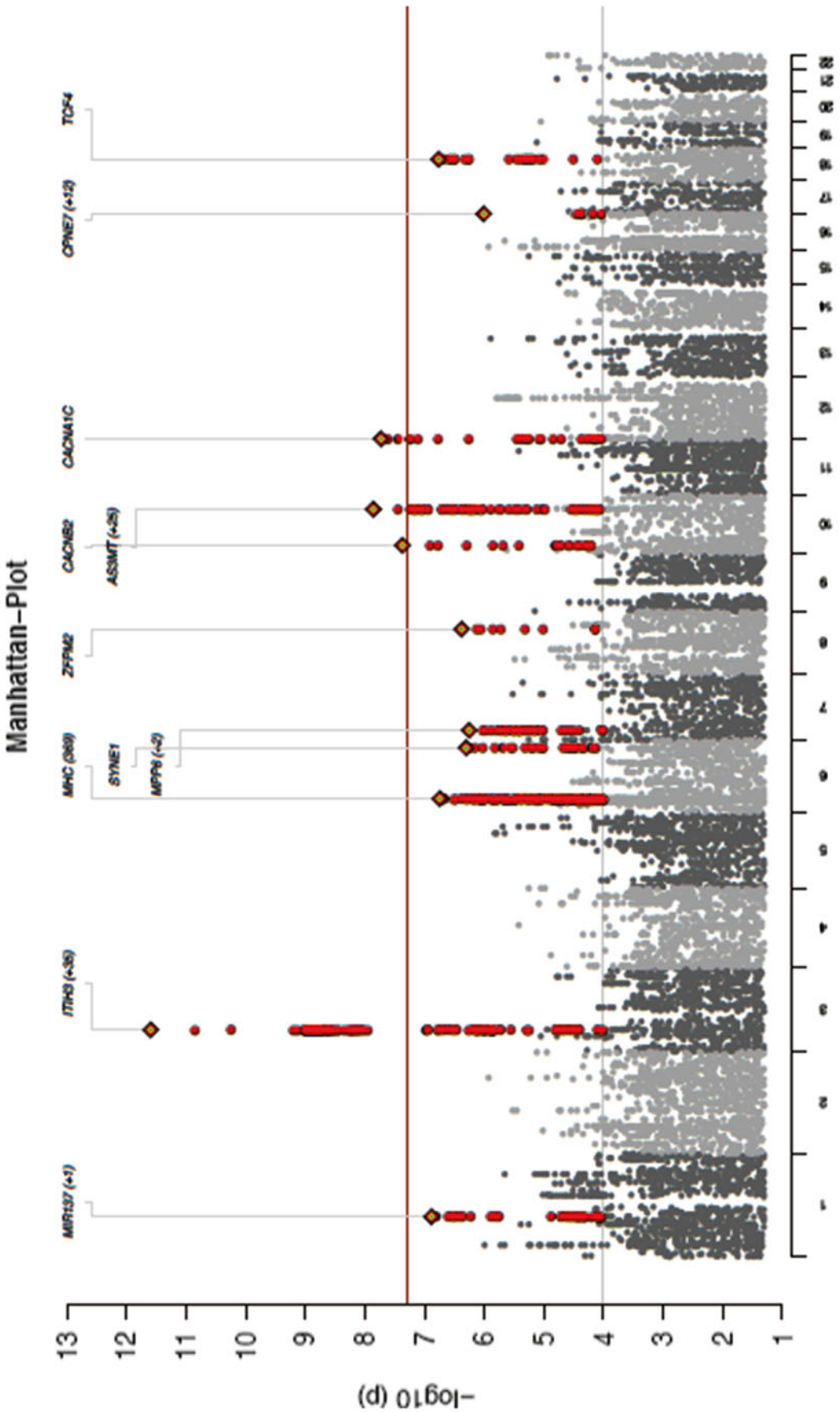

FIGURE 29.1 Results from a genome-wide association study of subjects with 5 major psychiatric disorders (schizophrenia, bipolar disorder, major depression, autism, and attention-deficit hyperactivity disorder). Data from >33,000 cases and >27,000 controls are represented here. Four genome-wide signals were found, including two genes coding for calcium channel subunits. Reprinted from the Lancet (18) copyright (2013) with permission from Elsevier.

the *de novo* events have appeared to be of more importance, at least for the childhood onset disorders. *De novo* status is demonstrated by examination of the parents' genomes and confirmation of the absence of the event in them.

29.1.8. High Risk Studies

Biochemical studies of individuals with psychiatric diseases are always confounded by the issue of disease effects: are biochemical differences between affected individuals and controls related to the cause of the disorder, or are they related to the effects of the disorder (or its treatment)? When investigating possible biochemical differences for a genetic disease, this difficult issue can be addressed by studying a group of individuals (usually adolescents or young adults) who are at high risk to develop the disorder under study (usually because they have parents and/or other relatives with the disorder). The high risk group may then be followed over time to assess whether the biochemical abnormalities observed are truly predictive of the disease.

29.1.9. Gene Expression and Other Genomic Approaches to Studying Psychiatric Disorders

Identifying genes for psychiatric disorders through classic genetic approaches has proven arduous, despite some recent successes mentioned in this chapter. This is due to the likely complex, polygenic nature of these disorders-multiple genes with variable penetrance involved in different subtypes of the illnesses. The imprecise nature of broad psychiatric phenotypes had also been a major rate limiting step (26–28), and is the subject of study of a new field, psychiatric phenomics (29, 30). Another major factor is heterogeneity at a SNP level—different SNPs in the same genes in different individuals and populations (10). In addition to heterogeneity, there is also a growing appreciation of the genetic, neurobiological and phenotypic overlap and interdependence of various major neuropsychiatric disorders (31, 32, 28). The use of endophenotypes and boot-strapping with other lines of work e.g., neurophysiology (33), imaging (34), and animal models (35), may provide for an accelerated pace of gene identification in the years to come.

The completion of the sequencing of the human genome and that of other model organisms, coupled with the advent of microarray technology over the last decade, have made large scale genomic studies scientifically and economically feasible. After some initial debate about different microarray platforms (36), there is an emerging consensus that different platforms perform with similar accuracy and reliability if employed well (37). The main room for improvement has been and is at the level of designing appropriate biological experiments, and integrating multiple independent lines of evidence in a Bayesian fashion. Human postmortem brain gene expression profiling studies from subjects with neuropsychiatric disorders have produced interesting leads (38–40). However, this important line of work, if pursued by itself, suffers from multiple caveats (41)—genetic variability, difficulty of building large enough cohorts, uncertainty about exact pre-mortem diagnosis, agonal artifacts (42), impact of co-morbid medical conditions, and the potential effects of environmental variables (medications, drugs of abuse, stress, nutrition) on brain gene expression changes. Animal model gene expression studies avoid these caveats, but suffer from the potential limited relevance of the animal model used to the human condition (43).

A combined approach, termed Convergent Functional Genomics (Figs. 29.1 and 29.2) which cross-matches human and animal model data, genetic and gene expression, has been developed as a way of avoiding the limitations of the individual approaches mentioned, and reinforcing their strengths in a Bayesian fashion (44). This approach has been applied with some success to bipolar disorder (35, 45), alcoholism (46), schizophrenia (47, 10), and anxiety disorders (48). Candidate genes identified by such an approach can be pursued in a prioritized fashion to obtain additional unambiguous evidence for involvement in the illness, through human sequencing studies and transgenic mouse studies. Moreover, the list of prioritized genes identified by approaches such as Convergent Functional Genomics also provides testable hypotheses for epistatic interactions among the co-expressed genes (35, 44).

More recently, there has been renewed interest in identifying peripheral correlates of neuropsychiatric disorders, termed biomarkers. There are to date no well established, specific clinical laboratory blood tests for psychiatric disorders. Given the complex nature of psychiatric disorders, the current reliance on patient self-report of symptoms and the clinician's impression on interview of patient is a rate limiting step in delivering the best possible care with existing treatment modalities, as well as developing new and improved treatment approaches, including new medications. Identifying molecules in the blood that reflect illness in the brain would be a major advance. These molecules could be used to develop clinical laboratory tests to aid: 1) diagnosis of illness, 2) early intervention and prevention efforts, as well as, 3) prognosis of course of illness, and 4) monitoring response to various treatments, including medications. In conjunction with other clinical information, such tests will play an important part of personalizing treatment to increase effectiveness and avoid adverse reactions. Moreover, they will be of immediate use to pharmaceutical companies engaged in new neuropsychiatric drug development efforts, at both a pre-clinical

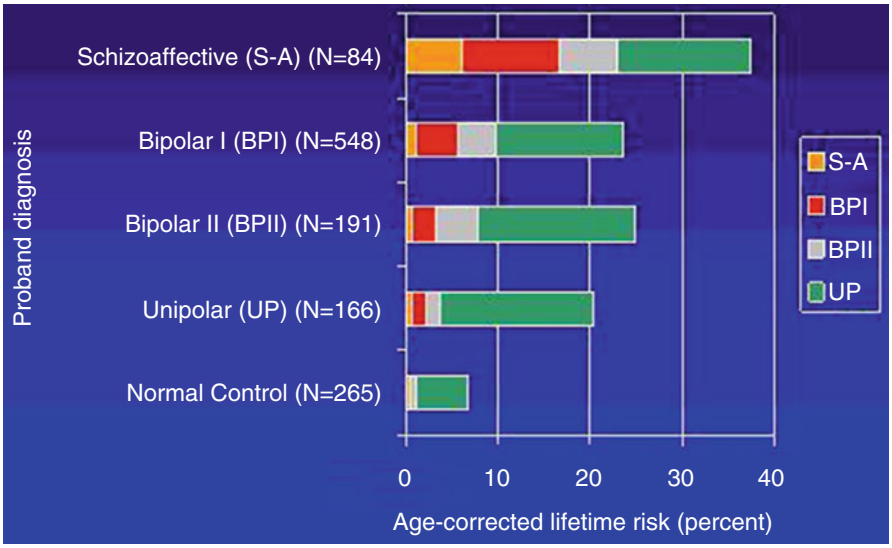

FIGURE 29.2 Age-corrected lifetime risk for relatives of subjects with schizoaffective disorder (S-A), bipolar disorder I (BPI), bipolar disorder II (BPII), unipolar disorder (UP) and normal controls for developing the disorders listed above.

and clinical (Phase I, II and III) stages of the process. Lymphocyte protein studies (35) and gene expression profiling (42, 49–52) have emerged as particularly interesting areas of research in the search for peripheral biomarkers. Most of the studies to date have focused on human blood gene expression profiling, comparison between illness groups and normal controls, and cross-matching with human postmortem brain gene expression data. They suffer from one or both of the following limitations: 1) the sample size used in most reports so far is small. Given the genetic heterogeneity in human samples and the effects of illness state and environmental history, including medications and street drugs, on gene expression, it is questionable if they have sufficient power to extract bona fide findings, despite the variety of sophisticated statistical methodologies used. Combined approaches, such as Convergent Functional Genomics, may be useful in terms of overcoming current limitations, 2) Use of lymphoblastoid cell lines, obtained from Fresh blood, with phenotypic state information gathered at time of harvesting, may be more informative than immortalized lymphocytes, and avoid some of the caveats of Epstein-Barr virus (EBV) immortalization and cell culture passaging. Some recent successes in biomarker discovery using Convergent Functional Genomics include identifying biomarker panels for mood state (53), psychosis state (hallucinations, delusions) (54) and suicidality (55). All these studies demonstrate predictive ability in independent cohorts, a key litmus test for any biomarker or genetic finding.

In conclusion, genomics has proven to be a useful partner to classic genetics approaches, and combined approaches may provide shortcuts to discovery of genes and overall understanding of the neurobiology involved. More progress in quantitative profiling of psychiatric phenotypes, and borrowing of concepts and paradigms from other medical fields that are farther along, such as cancer genetics and genomics, are exciting areas of advance for the near future. It is hoped that together, all these approaches will provide in the long term a sound scientific basis for the development of personalized medicine in psychiatry (56).

29.2. Epigenetics of Psychiatric Disorders

Epigenetics is the study of heritable biological modifiers of DNA transcription (57, 58). The most common mechanisms discussed are 1) DNA methylation, and 2) chromatin remodeling. Methylation of DNA effectively prevents transcription of a particular gene. Chromatin (the protein framework supporting DNA in the nucleus) may exist in an active state (allowing transcription) or an inactive state (preventing transcription). Various stimuli, including environmental events, may be responsible for epigenetic changes that turn genes on or off. Of course, substantial additional gene regulation occurs at the level of RNA transcription, including by regulatory micro RNAs (miRNA), much of which may be captured by the gene expression studies summarized in another section of this chapter.

Epigenetic mechanisms have not been demonstrated to be critical in clinical studies of traditional psychiatric disorders to date. Of note a genomewide methylation scan in brain DNA from subjects with major depression and controls was recently published (420); findings were regarded as exploratory. A review by Menke et al. (59) describes studies in the gene families coding for elements of the hypothalamic-pituitary-adrenal axis and also the neurotrophin system. Among other diseases, differential methylation does appear to be important in Prader-Willi syndrome, which includes mental retardation and sometimes mood disorders as part of the clinical picture. This condition is related to imprinting on 15q; the DNA segment for this chromo-

somal region that is transcribed is generally the segment from the father. The mother's DNA from that region tends to be methylated and not transcribed. In Prader-Willi there is deletion of the father's DNA in that region as well, so neither segment is functional. In Angelman syndrome the same chromosomal region is deleted in the DNA from the mother (and sometimes there is duplication of the father's chromosome, or uniparental disomy).

Two animal models are of some interest. One has been described by Eric Nestler, and includes differential methylation (and perhaps chromatin remodeling) in social defeat, with susceptible mice demonstrating decreased BDNF and cyclic AMP response element binding protein (CREB), and thus presumably decreased neuronal growth. This is preventable with chronic antidepressant treatment. (60, 61) The other model [studied by Frances Champagne at Columbia (62, 63)] involves maternal licking/grooming in rodents. Low licking/grooming is associated with increased methylation of the estrogen receptor promoter in the offspring, decreased production of that receptor, and many behavioral changes suggesting greater responsivity to stress (but also increased sexual interest and more offspring). The most interesting aspect of this model is that the differential methylation appears to be transmitted to the F2 generation as well. This is an unusual instance of "inheritance of acquired characteristics," or one example that would seem to support the discredited theories of Lamarck.

29.3. Mood Disorders

29.3.1. Genetic Epidemiologic Studies

29.3.1.1. Family Studies

Family studies in Mood disorder have continually demonstrated aggregation of illness in relatives (64). In a study at NIMH, 25% of relatives of bipolar (BP) probands were found to have bipolar or unipolar (UP) illness themselves, compared with 20% of relatives of unipolar probands and 7% of relatives of controls (65) (Tables 29.1, 29.2; Fig. 29.2). In the same study 40% of the relatives of schizoaffective probands demonstrated Mood illness at some point in their lives. These data demonstrate increased risk in relatives of patients; they also show that the various forms of Mood illness appear to be related in a hierarchical way: relatives of schizoaffective probands may have schizoaffective illness themselves, but are more likely to have bipolar or unipolar illness. Relatives of bipolar probands have either bipolar or (more likely) unipolar illness.

Age of onset may be useful in dividing Mood illness into more genetically homogeneous subgroups (66). Early onset probands have increased morbid risk of illness in relatives in some data sets. Other subphenotypes, such as cycling frequency and comorbid anxiety disorders or substance use disorders, have also been studied (see below).

A birth cohort effect has been observed in recent family studies: there is an increasing incidence of Mood illness among persons born more recently. The cohort effect appears to be true for schizoaffective and BP illness as well as UP (67). The cohort effect is true among relatives at risk to a greater degree than in the general population, an observation that may be ascribed to a gene by environment interaction. The critical environmental variable(s) are at this time not known.

TABLE 29.1 Lifetime risk for major affective disorder in different groups.

General population	2%
Relatives of UP	20%
Relative of BP	25%
Relatives of SA(BP)	40%
Children of two ill parents	50%+
Identical twin ill	60%

TABLE 29.2 Lifetime risk for bipolar disorder in different groups.

Controls	0.5–1%
Relatives of UP	3%
Relatives of BP	8%
Relatives of SA	17%
MZ twin	80%

29.3.1.2. Twin Studies

Twin studies show consistent evidence for heritability. On the average, monozygotic twin pairs show concordance 65% of the time and dizygotic twin pairs 14% of the time (68). When divided by polarity, twin probands with bipolar Illness show about 80% concordance (69, 70). Bienvenu et al. (71) summarize three recent twin studies of bipolar disorder and calculated a heritability of 85%. This implies that about 85% of the variance in whether a person in the population will experience bipolar disorder is explained by genetic factors. This rate of heritability in bipolar disorder is higher than other psychiatric illnesses and most complex medical conditions.

29.3.1.3. Adoption Studies

Several adoption studies have been performed in the area of Mood illness: the results have been generally consistent with genetic hypotheses (72).

29.3.2. The Mood Spectrum (Types of Mood Disorders and Other Disorders That Are Genetically Related)

BPI—Classic "manic-depressive illness" with severe mania, generally including episodes of major depression as well.

BPII—This disorder is genetically related to BPI and UP. There is some evidence in family studies for an excess of BPII illness in relatives of BPII probands (73). It has been demonstrated that BPII tends to be a stable lifetime diagnosis (that is, patients do not frequently convert to BPI).

Rapid cycling—Rapid-cycling BP illness has been the subject of great theoretical and clinical interest. A link with thyroid pathology has been proposed. Rapid-cycling appears to arise from factors which are separable from the genetic vulnerability to BP illness and which do not lead to aggregation within families. However, "rapid switching" of mood, which is related, appears to be familial (74).

UP mania—This entity includes BPI patients with no history of major depression. This group is not distinguishable from other BPI patients on the basis of family pattern of illness.

Cyclothymia—This condition of repetitive high and low mood swings, generally not requiring clinical attention, may be genetically related to BP disorder (75).

Schizoaffective disorder—A group of patients with intermittent psychosis during euthymia have an increase in mood disorder in relatives and an increase in schizophrenia in relatives. This group may have the highest genetic load (total risk for mood disorder or schizophrenic illness in relatives) of any diagnostic category (76). They may carry genes related to both bipolar illness and schizophrenia. Patients with chronic psychosis and superimposed episodes of mood disorder also confer risk for both chronic psychosis and mood disorder to relatives but have less overall genetic load.

Schizophrenia—An overlap in linkage areas and vulnerability genes has been identified in recent years, especially in genes related to glutamate neurotransmission (see below).

Eating disorders—Family studies of anorexia and bulimia have generally found excess mood disorder in relatives. Relatives of anorexics may have similar risk for mood disorders to that of relatives of BP probands (68).

Attention-deficit disorder—Children with this disorder appear to have increased depression in their relatives. The opposite has not been demonstrated (BP/UP probands have not been reported to have increased risk of attention deficit disorder in their offspring) (72).

Alcohol dependence—There may be overlapping vulnerability traits. Alcoholism appears to be comorbid with UP and BP disorders (each appears to confer an increased risk for the other within individuals). There is some evidence that alcoholism with Mood disorder may itself aggregate within families (77).

29.3.3. Linkage Studies

Linkage has been demonstrated on 4p, 6q, 8q, 13q, 18p, 18q, and 22q. Other areas are "close" to significant, including 12q, 21q, and Xq (78).

29.3.4. Endophenotypes

A number of such markers have been suggested, including:

- REM sleep induction by cholinergic drugs,
- white matter hyperintensities on MRI,
- amygdala activation on fMRI
- hippocampal size,
- response to tryptophan depletion,
- response to sleep deprivation.

See review in Hasler et al. (78).

29.3.5. Gene Expression Studies

See Elashoff et al. (79) for information.

29.3.6. High Risk Studies

More offspring of patients than controls have a diagnosed Axis I disorder. Offspring of BP parents may be more prone to respond to dysphoric feeling states by "disinhibitory" behavior (80).

We have published an initial report on the characteristics of 141 high-risk cases and 91 controls (81). All cases were ascertained because of their relationship to a proband with severe bipolar disorder and because they were in the age range 12–21. Among case subjects manifesting a major affective disorder (n = 33), there was an increased risk for anxiety and externalizing disorders in comparison to cases without mood disorders. In cases but not controls, a childhood diagnosis of an anxiety disorder [Relative Risk (RR) = 2.6 (1.1–6.3), p = 0.039] or an externalizing disorder [RR = 3.6 (1.4–9.0), p = 0.007] was predictive of later onset of major affective disorder. We believe that the idea of clinical diagnostic predictors has considerable translational salience. This provides guidance for clinicians on the prognosis of common childhood disorders, and on the importance of family history in developing prognostic assessments and monitoring strategies

29.3.7. Association/Candidate Gene Studies

Numerous candidate gene studies are now in the literature for bipolar illness. A few genes have emerged with replicated findings, or positive meta-analyses from multiple studies (Tables 29.1 and 29.2). We should note, however, that, in general, specific candidate genes have not been supported by genome-wide association studies to date (82). This may be an issue of genetic heterogeneity (different SNPs in the same gene, in different individuals or different populations), sample size, or it may indicate that many candidates are false positives despite their evidence in individual studies (82). We will feature these here.

D-Amino Acid Oxidase Activator (DAOA), formerly known as G72 (83–85): This gene is one of two implicated together in association studies on chromosome 13q. The gene G30 is a DNA sequence which is reverse transcribed within G72. The association was first identified by Hattori et al. (83) after work performed by Chumakov and colleagues in schizophrenia. It has been replicated by three other independent groups. The most recent work, by Williams et al. (86) shows association not only with bipolar illness, but with a subset of subjects with schizophrenia who also had clear mood episodes. The function of DAOA, or G72, is to oxidize serine, which is a potent activator of glutamate transmission via a modulatory site on the NMDA (N-methyl-D-aspartate) receptor. Thus inadequate DAOA function might be hypothesized to lead to problems in modulating the glutamate signal in areas of the brain such as the prefrontal cortex. Existing evidence from animal studies suggests that glutamate antagonists may have antidepressant effects, and that depression may be associated with inadequate modulation of glutamate neurotransmission.

Brain-derived Neurotrophic Factor (BDNF) (87, 57, 58, 88–90): This gene is a candidate based both on position (11p14, near reported linkage peaks in several family series) and function (as a neuronal growth factor, it is implicated in several recent theories of depression and bipolar mood disorder). BDNF has shown significant association in three independent reports in family-based data, but not in several case-control series. Two reports have suggested association in child/adolescent onset bipolar

disorder, and two additional series show association in rapid-cycling subgroups of bipolar patients. Several studies have shown that antidepressant administration is associated with increased central BDNF levels in experimental animals, and administration of BDNF itself has been associated with antidepressant-like activity. Depression has been postulated to be associated with decreased neurogenesis in the hippocampus, which is dependent on neurotrophic factors, including BDNF. Mood stabilizing medications used in bipolar illness are thought to have neuroprotective effects.

Disrupted in Schizophrenia 1 (DISC1) (91, 92): This gene on chromosome 1q was identified in a Scottish family with a genetic translocation and with multiple cases of psychiatric disorders, primarily schizophrenia. However, DISC1 variants were associated with mood disorders in family members as well. Later studies in an independent series of bipolar patients in Scotland were positive for association as well. A study in Wales of schizoaffective patients showed a linkage peak in the same chromosomal location. This gene is expressed in multiple brain regions, including the hippocampus, where it is differentially expressed in neurons. It is associated with microtubules; in mice, disruption of DISC1 leads to abnormal neuronal migration in the developing cerebral cortex. DISC1 appears to interact with phosphodiesterase 4B, which may play a role in mood regulation.

5HTT, MAOA, COMT (93, 94, 32): These three genes have been shown in metaanalyses to be associated with bipolar disorder, even though no strong effects were shown in any one study. The effect size for each appears to be in the range of 10–20% increase in risk. Each of these genes has been shown to be associated with other behavioral phenotypes, and each has been reported to interact with environment to increase risk for specific disorders (major depression, antisocial personality disorder, and schizophrenia respectively).

P2RX7 (aka P2X7, P2X7R) (95): This gene on 12q24 was identified in a French-Canadian case-control series following linkage studies using large pedigrees from the same population. It is a calcium-stimulated ATPase. The data are suggestive, but it awaits replication in an independent study.

GRK3 (96): The only candidate identified using animal model studies (a mouse model employing methamphetamine). The original gene expression studies were followed up by association studies in several samples as well as expression studies in human lymphoblasts. This gene participates in down-regulation of G protein coupled receptors.

29.3.7.1. Genome-Wide Association Studies in Bipolar Disorder

GWAS methods have now proven to be useful in psychiatric disorders, with several loci meeting stringent criteria in both schizophrenia and bipolar disorder (7, 8). Several of the loci described previously are the product of GWAS investigations (e.g., ANK3, CACNA1C, NCAN).

Ankyrin 3 (ANK3): The first gene identified in a major psychiatric disorder using GWAS methods was ankyrin 3 (97–99) This gene codes for a structural membrane protein related to sodium channels. Sodium transport has been reported to be abnormal in studies of bipolar disorder and major depression since the 1960s (100).

The calcium channel gene *CACNA1C* reached genome-wide significance in the report of Ferreira et al. (97). Recent data show *CACNA1C* with the most significant association results for any gene in a 16,000 subject consortium analysis of bipolar GWAS data (8).

NCAN was recently identified by a large international consortium studying bipolar illness and using GWAS methods (101). It codes for an extracellular matrix glycoprotein. In the mouse, this is localized in cortical and hippocampal brain areas.

A report from the Psychiatric GWAS Consortium BP Working Group included data from nearly 12,000 BP cases and 52,000 controls (16). Several specific SNPs showed genome-wide significant association with BP, most prominently variants in CACNA1C (which codes for a subunit of an L-type calcium channel). Of the 34 SNPs most highly associated with BP in the primary dataset, 31 showed the same direction of effect in the replication dataset, suggesting that the findings are true signals with many more remaining to be identified.

29.3.7.2. Sequencing Studies in Bipolar Disorder

Several thousand subjects are currently being studied using methods to sequence the entire exome (the transcribed segments of the genome) or the whole genome. A Bipolar Sequencing Consortium has begun to hold regular meetings in which to share data. Among the early results is a collection of sequence variants in CACNA1C and other calcium channel genes.

29.3.7.3. CNV Studies in Bipolar Disorder

Rare CNVs were reported to be elevated in a study by Zhang et al. (102) in subjects with bipolar disorder from the NIMH Genetics Initiative Database. A subsequent study showed increased CNVs in patients with bipolar disorder who had early onset (≤21), but not patients with later onset (103). However, other studies have not seen an elevation in CNVs (104). In order for these reports to be biologically meaningful, the identification and confirmation of specific loci, or genes, involved in the putative increased CNV burden in bipolar illness, will be necessary. One study has implicated 16p11.2 (105) and one study has reported increased CNVs in the *GSK3beta* gene (106) in bipolar disorder. CNVs may now be detected using dedicated microchips, and thus these studies are expected to be more commonly performed in the future.

29.3.8. Empirical Data for Genetic Counseling

Molecular genetic studies hold great promise in the future for families with Mood disorder, particularly BP disorder. Genetic risk score methods are currently being tested (107). However, genetic counseling currently is based on empirical risk figures.

The lifetime risk for severe (incapacitating) Mood disorder is about 7%. Risk is increased to about 20% in first-degree relatives of UP patients, and 25% in first-degree relatives of BP. It appears to be 40% in relatives of schizoaffective patients. The risk to offspring of two affected parents is in excess of 50% (Tables 29.1, 29.2; Fig. 29.2). Overall risk figures appear to be rising in recent years, but more so in relatives of patients than in the general population (keeping at about a 3:1 ratio). Average age of onset is about 20 for bipolar disorder and 25 for unipolar.

29.4. Alcoholism

29.4.1. Epidemiologic Genetic Studies

29.4.1.1. Twin Studies

Twin studies tend to show heritability of drinking behavior and heritability of alcoholism. The normal twin studies of drinking behavior are well summarized by Murray et al. (108, 109). The Finnish twin study of Partanen included interview data on 902 male twins between 28 and 37 years of age. Heritability was 0.39 (i.e. about 39% of the variance between members of a twin pair is due to genetic factors) for frequency of drinking and 0.36 for amount consumed per session. A second Finnish study by Kaprio et al. (110) included data on several thousand pairs of twins in the state twin registry. Overall heritability for total alcohol consumption was 0.37 in males and 0.25 in females. Clifford et al. (111) report a study in which 572 twin families from the Institute of Psychiatry register were examined (including a total of 1742 individuals). Additive genetic factors were found to account for 37% of the variance in alcohol consumption among drinkers, when pedigree data are considered together with twin data and the effect of shared environment on twin concordance is accounted for. The critical data from these three large twin studies are strikingly similar, at least in males.

Twin studies of alcoholism itself have generally shown heritability. Kaij (112) studied registration of twin subjects at the Swedish County Temperance Boards. Such registration implies that a complaint was made about a person's behavior while drinking, either by the police or a third party. This would not generally include alcoholics who were socially isolated, though they might be significantly impaired. The registration information was followed up with personal interviews of probands and co-twins. In a total of 205 twin pairs, probandwise concordance was 54.2% in MZ's and 31.5% in DZ's ($p < .01$). Concordance rates in MZ's increased with the severity of the disturbance. A reanalysis of these data by Gottesman and Carey (113) shows heritability to vary from 0.42 to 0.98 with the more serious forms of alcoholism being more heritable.

Kendler et al. (114) conducted a population-based study of female twin pairs from the Virginia twin registry. Personal interviews were completed on 1033 of 1176 pairs. MZ concordance varied from 26% to 47% (narrow to broad definition of alcoholism) while DZ concordance ranged from 12% to 32%. Calculated heritability was 50–61%. This suggests substantial genetic influence in alcoholism in women in the populations studied.

29.4.1.2. Adoption Studies

Goodwin et al. (115) compared 55 adopted-away male children of an alcoholic parent with 78 adoptees without an alcoholic parent. The groups were matched by age, sex, and time of adoption. The principal finding was that 18% of the proband group were alcoholic compared with 5% of the controls ($p < 0.02$). Goodwin also compared adopted-away sons of alcoholics with sons of alcoholics raised by the alcoholic parent (116). There was no difference.

Bohman (117) used state registers in Stockholm to study 2324 adoptees born in that city between 1930 and 1949. Male adoptees whose fathers abused alcohol (excluding those who were also sociopathic) were more likely to be alcoholic themselves (39.4% vs 13.6%, $p<0.01$) compared with adoptees without an alcoholic (or sociopathic) father. Cloninger, Bohman, and Sigvardsson (118) then reanalyzed Bohman's data set, and postulated a familial distinction of alcoholics: the milieu-limited (type I) and male-limited (type II) groups. Type I alcoholics [as defined in Cloninger, (119)] usually have onset after age 25, manifest problems with loss of control, and have a great deal of guilt and fear about alcohol use. Type II alcoholics have onset before age 25, are unable to abstain from alcohol, and have fights and arrests when drinking, but less frequently show loss of control and guilt and fear about alcohol use. Cloninger reanalyzed the Stockholm Adoption data using these specific categories. This analysis showed that Type I alcoholics were significantly increased in prevalence only among those adoptees with both genetic and environmental risk factors (alcoholism in both biologic and adoptive parents). Type I was the most common type of alcoholism, however, being present in 4.3% of the controls with no risk factors. Type II alcoholism was present in only 1.9% of the controls but 16.9–17.9% of adoptees with genetic risk factors, whereas the presence or absence of environmental risk factors (alcoholism in adoptive parents) did not appear to make a difference.

Bohman et al. (120) extend this finding to women adoptees, identifying as particularly important the incidence of alcoholism in the biologic mothers of these adoptees.

29.4.1.3. Family Studies

Family studies of alcoholism have been reviewed by Cotton (121) and Goodwin (122). Both reviews concluded that there is a concentration of alcoholics in the families of alcoholic probands. Cotton (summarizing 39 studies on families of 6251 alcoholics and 4083 nonalcoholics) reports an overall prevalence of 27.0% alcoholism in fathers of alcoholics and of 4.9% in mothers; 30.8% of alcoholics had at least one alcoholic parent. The same preponderance of alcoholism was not seen in the parents of comparison groups of patients with other psychiatric disorders. The studies of nonpsychiatric controls reviewed in the same study show a rate of 5.2% in fathers and 1.2% in mothers. Nurnberger et al. (123) published a large recent family study from the Collaborative Study of the Genetics of Alcoholism (COGA). Risk to relatives was elevated by a factor of two or greater, depending on the definition of alcoholism. However, alcohol abuse did not seem to be increased in relatives of probands with alcohol dependence, suggesting that a lifetime diagnosis of DSM-IV alcohol abuse does not arise from the same genetic factors as DSM-IV alcohol dependence.

29.4.2. Disorders Genetically Related to Alcoholism

Winokur et al. (124) reported an increased prevalence of depression in the female relatives of alcoholics roughly comparable to the increased prevalence of alcoholism in male relatives. There may be some forms of illness that result from shared vulnerability factors. Recent studies suggest that comorbid disorders (including features of alcoholism and Mood illness) may themselves run in families.

Bohman et al. (120) and Cloninger et al. (125) have observed that adopted-away daughters of Type II (male-limited) alcoholics manifest no increase in alcoholism but do show an increase in somatization disorder.

It is not possible to conclude at this time that a single genetic predisposing factor may be manifest as either alcoholism or sociopathy. However, some sociopathic alcoholics may transmit both alcoholism and sociopathy as part of the same syndrome.

Earls et al. (126) report an increase in DSM-III behavior disorder in general (attention deficit disorder with hyperactivity, oppositional disorder, and conduct disorder) in offspring of alcoholic parents. The risk was greater for offspring of two alcoholic parents than for those of one alcoholic parent.

Cadoret et al. (127) report that drug abuse in adoptees is associated with alcohol problems in first degree biologic relatives.

Nurnberger et al. (123) found substance dependence, several anxiety disorders, and major depression increased in the relatives of probands with alcohol dependence.

29.4.3. Linkage Studies

Several linkage studies have been completed in sizeable populations. Genes predisposing to alcohol dependence appear to be located on chromosomes 1, 2, 4, 7, and 16 (128, 129).

29.4.4. Association Studies

GABRA2: Variants in GABRA2 on chromosome 4p have been shown by Edenberg and colleagues in COGA to be associated with the power of *beta* oscillations in the EEG (which are inversely related to inhibitory neuronal activity in the cortex) and to alcohol dependence (130).

The association with alcohol dependence has now been replicated by four other groups. This gene appears to be particularly strongly related to vulnerability to problems with impulse control, as the risk allele is seen in adolescents with conduct disorder and in those alcohol dependent persons who also have drug dependence (131). Other GABA receptor genes, such as GABRG3 may also be associated with alcohol dependence (132).

ADH4: ADH (alcohol dehydrogenase) is the major metabolic enzyme for alcohol, catalyzing its breakdown into acetaldehyde, which is then further metabolized by aldehyde dehydrogenase (ALDH). Both ADH and ALDH have variants that have been associated with the "flushing" reaction to alcohol (a feeling of warmth that is accompanied by reddening of the skin and sometimes nausea and tachycardia). These variants are most common in East Asian populations and they tend to protect against the development of alcohol dependence. In recent studies, single nucleotide polymorphisms in some of the ADH enzymes (genes for several isoenzymes of ADH are located on chromosome 4q) have been associated with alcohol dependence in Caucasian populations and in Native Americans. The strongest finding is in ADH4 (133), and this appears to be associated with early onset of regular drinking (unpublished data). Recent data also show variants in ADH1B related to alcohol dependence in European-American and African-American populations (134).

CHRM2: The M2 muscarinic receptor gene on chromosome 7q is associated with alcohol dependence and major depression in the COGA sample, and this association has been independently replicated (135). The association with depression recalls the cholinergic-adrenergic balance hypothesis of Janowsky and colleagues from the 1970s (a relative increase in central cholinergic activity is associated with depression and a relative increase in central adrenergic activity with mania) (136).

TAS2R16: This gene, located under the same linkage peak on 7q as CHRM2, codes for a bitter taste receptor. Variants are associated with alcohol dependence, which is consistent with studies showing that relative sensitivity to sweet taste is related to alcohol acceptance in rodent models. The risk gene variant in human studies is much more common in African-Americans than in European-Americans (137).

DRD2: Originally reported about a decade ago, the literature on DRD2 is still controversial. A meta-analysis of 21 studies shows an increased risk of 50–100% for persons carrying the A1 allele (138). However, recent work has demonstrated that this polymorphism may actually be reflecting variation in ANKK1, a gene next to DRD2 (139).

29.4.5. Genomewide Association Studies

GWAS studies of modest size (~1000 cases and ~1000 controls) have been reported using phenotypes related to alcohol dependence and alcohol consumption (140–146). In general these studies have not achieved enough power to clearly demonstrate and confirm genomewide significant results. A meta-analysis in this area is in progress, and the Psychiatric Genomics Consortium has identified alcohol dependence and other substance abuse diagnoses as areas of priority for attention over the next several years (147, 148).

29.4.6. Etiologic Marker Studies

Major areas of concentration in the search for a potential biologic trait marker of alcoholism include 1) enzymes of alcohol metabolism and other enzymes, 2) EEG and evoked potentials before and after alcohol, 3) psychologic/psychophysiologic differences, 4) behavioral and neuroendocrine responses to alcohol.

Alcohol is primarily metabolized in the liver by the enzymes alcohol dehydrogenase (ADH) and aldehyde dehydrogenase (ALDH). Four isozymes of ALDH are known. Three are found in the cytoplasm and one (ALDH2) in the mitochondria. It is the latter that is probably responsible for most acetaldehyde metabolism in vivo (150). The ALDH2 enzyme is lacking in about 50% of Japanese subjects tested (149) and apparently in other Oriental groups as well. Such people are subject to the "flushing" reaction from alcohol (similar to a disulfiram reaction). Alcohol elimination is not different in such subjects. However, the alcoholism rate is significantly diminished.

Monoamine oxidase (MAO), a primary catabolic enzyme for dopamine, norepinephrine, and serotonin (among other substrates), has been reported to be lower in alcoholic subjects than in controls (151–154). Major et al. (154) report reduced MAO activity in liver

but not brain samples from chronic alcoholics. Perhaps most interesting is the report from von Knorring et al. (155), suggesting that low MAO is related only to Type II alcoholism. Confirmatory evidence was reported by Sullivan et al. (156).

A poorly synchronized resting EEG (lower alpha) has been thought to be related to a predisposition for alcoholism (157). Change in alpha rhythm following alcohol is more concordant in monozygotic than dizygotic twins (as are multiple other EEG parameters) (158, 159). A relationship was found between resting EEG of the unselected twins and drinking behavior (less alpha in the twins who drank more). In subsequent work, Propping et al. (160) found that relatives of alcoholics with poorly synchronized resting EEGs demonstrated the same characteristic themselves. Change in alpha rhythm following alcohol was also found to differentiate young adult subjects at high risk for alcoholism from controls (161).

Measurements of event-related potentials have shown smaller P300 waves following visual stimuli in 7–13 year old sons of alcoholics compared to controls (162) lessening the likelihood of previous alcohol exposure. Similar findings using an auditory stimulus had been reported in an older group (age 21–26) both before and after alcohol administration (163). Hill et al. (164) found a significant increase in P_{300} latency in adolescent and adult relatives of alcoholics compared to controls. The EEG/ERP area remains one of the more promising in the field of pathophysiologic markers for alcoholism. Recent single gene discoveries noted above for GABRA2, ADH, and CHRM2 were mediated in part by data from electrophysiologic phenotypes.

Schuckit has studied behavioral and neuroendocrine responses to alcohol infusion in a series of high-risk populations. Offspring of alcoholics displayed less subjective intoxication, than controls (165–167). A follow-up study by Schuckit (168) shows that decreased subjective intoxication is correlated with later development of alcoholism in sons of alcoholics.

29.4.7. Summary

There appear to be hereditary factors operative in normal drinking behavior and in the vulnerability to alcohol abuse. The "flushing" reaction to acetaldehyde is one of the clearest instances of pharmacogenetic variants that influence human behavior, though even here the interaction between genotype and environment in different ethnic groups may result in very different outcomes (169). Alcoholism clearly runs in families. It is more often manifest in men than in women. The familial preponderance is primarily related to genetic factors and the differentiation by gender is primarily the result of sociocultural factors. There may be two distinct types of alcoholism with different patterns of inheritance, Type I (or milieu-limited) and Type II (or male-limited). Type II alcoholism is more severe and more likely to be strongly influenced by major gene effects.

Single genes related to alcohol dependence have now been identified, and they appear to operate by independent pathways. GABRA2 alleles appear to increase risk for conduct disorder in adolescents and later be associated with alcohol dependence. ADH4 alleles may be related to tolerance of alcohol and subsequent alcohol problems. CHRM2 variants may predispose to alcohol problems by way of the comorbid conditions of depression and anxiety (170). Large GWAS meta-analyses are in progress and show promise for the identification of additional common variants and pathways related to alcohol dependence.

29.5. Alzheimer's Disease

The neuropathology of AD includes accumulation of amyloid plaques, which are aggregates of an abnormal amyloid fragment, termed abeta 1–42. There are also neurofibrillary tangles, a major constituent of which are phosphorylated forms of tau. The ratio of Abeta 1–42 and phosphotau in CSF has substantial predictive diagnostic value in the clinical evaluation of mild cognitive impairment, a clinical state which often progresses to dementia.

Genetic etiologies for some forms of Alzheimer's are now clear. Specific genes that influence vulnerability have now been identified. A review of the epidemiologic studies, however, is remarkable in that it does not show high heritability of the disorder. This is partially attributable to multiple etiologic factors, environmental as well as genetics. It is also related to the variable age of onset for the condition. Early onset cases are more likely to be heritable, and may be determined by single genes. Later onset cases are more likely to be multifactorial. Important genetic factors in late onset cases may be obscured by the fact that mortality from other causes decreases familial aggregation.

29.5.1. Twin Studies

A total of 81 twin pairs, where at least one member is affected with Alzheimer's Disease, (AD) have been reported in the literature. The MZ concordance rate (approximately 45%) is not different from the DZ concordance rate (approximately 35%) in these studies.

29.5.2. Family Studies

Many of the relatives of later onset AD probands will have died of other causes before passing the age of risk. Breitner and Folstein (171) reported that the first-degree relatives of demented subjects with amnesia, apraxia, and aphasia have a corrected lifetime risk of close to 50% for AD at age 90, compared to 7% for relatives of controls (demented subjects without agraphia).

There are divergent opinions concerning the degree to which AD is familial, depending upon the age of onset and clinical characteristics. A subset of early onset AD cases are highly familial. At least some AD cases (primarily those with later onset) are sporadic.

29.5.3. Linkage Studies

In 1987, St. George-Hyslop et al. (172), reported linkage of familial AD to RFLP markers on chromosome 21. The peak LOD score of 4.25 was suggestive of a causative gene near these markers. Subsequently, several studies have identified isolated, rare AD families in which a point mutation in the gene for amyloid precursor protein has been found in ill pedigree members (173, 174). These studies suggest that abnormalities in this gene (which produces a proteinaceous material found to accumulate in the extracellular space in brains of persons with AD) can cause the disease by itself. Another cause of early onset familial Alzheimer's is a gene on chromosome 14 (175). Additional families are linked to a gene on chromosome 1. The genes on chromosomes 1 and 14 code for proteins named presenilins and appear to be highly homologous. They are termed presenilin 1 and 2, respectively. Mutations in these genes cause rare, early-onset forms of AD.

Many late onset families may show linkage to a region of chromosome 19 coding for lipoprotein E (ApoE), which is also implicated in cardiovascular illness. ApoE has 3 common alleles, termed 2, 3 and 4. One copy of the E4 allele will increase risk threefold compared to those with E2/E3. Two copies of E4 increase risk by a factor of 10–15. ApoE does not appear to be as strong an AD risk factor in African populations, though it is present in African-Americans (176). Differences may be related to diet and other environmental factors associated with lipid metabolism and vascular damage. The molecular mechanisms for the Alzheimer's vulnerability genes are now the subject of intense investigation. There is reason to suspect that these risk alleles may have an effect on accumulation of amyloid and an abnormal phosphoprotein, termed, tau, a constituent of microtubules.

Apart from the large effect size of ApoE alleles, the remaining common risk alleles for AD have comparatively small influences on risk. The Alzheimer Disease Genetics Consortium (ADGC) performed a genome-wide association study, identifying 19 loci harboring AD risk alleles of small effect (421). Among the mechanisms implicated are immune processes, trafficking of amyloid, hippocampal synaptic function, cytoskeletal function and axonal transport, regulation of gene expression and post-translational modification of proteins, and microglial and myeloid cell function.

29.6. Antisocial Personality Disorder

29.6.1. Epidemiologic Studies—Twin Studies

In a Danish twin study 32.6% (28/86 pairs) of MZ twins were concordant for criminal behavior, compared to 13.8% (21/152 pairs) of DZ twins ($P < .001$). In a Norwegian twin study, Dalgard and Kringlen (177) found a higher MZ concordance (8/31 pairs or 25.8%) for crime compared to the DZ concordance (8/54 pairs or 14.8%), but this failed to reach statistical significance ($P = 0.11$).

Schulsinger (178) and Crowe (179) conducted adoption studies of antisocial personality disorder (AP). In these early studies, there was a consistent observation that the adopted-away offspring of AP biologic parents had a higher risk for AP behavior than did control adoptees. For example, 6/46 adoptees of female felons met criteria for AP compared to 0/46 control adoptees (179). In this study, outcome was unrelated to the length of time the adoptees remained with their biologic mothers. In Schulsinger's study of 57 adoptee AP and 57 control probands, AP was found among 3.9% (12/305) of biological relatives of AP adoptees, compared to 1.4% (4/285) of biological relatives of control adoptees, a highly significant difference. If only the fathers were considered, 9.3% of the probands' biological fathers (5/54) received a diagnosis of AP compared to 1.8% of the biological fathers of control adoptees. In a larger study, using adoption and criminal registries, Mednick et al. (180) reported that when neither the biologic nor adoptive parents had been convicted, adoptees had a conviction rate of 13.5%. If only the adoptive parents were convicted, the adoptee conviction rate rose to only 14.7%. If only the biologic parents were convicted, the adoptee conviction rate was 20%. When both sets of parents had been convicted, the conviction rate for adoptees was 24.5%. The risk for conviction in a male adoptee increased as a function of the number of convictions in his parents.

These findings were confirmed in a later study of criminality using a cohort of adoptees from Bohman et al. (120). They reported that both genetic and "postnatal" influences were detectable in the risk for AP. When postnatal factors predisposed to criminality, 6.7% (8/120 male adoptees) were criminal compared to 2.9% (19/666) of male adoptees with non-predisposing postnatal and genetic backgrounds. When the genetic background, but not the postnatal environment, was predisposing, 12.1% of male adoptees were criminal compared to 2.9% of control male adoptees. When both the genetic and postnatal background were judged to predispose to criminal behavior 40.0% of male adoptees were criminal. These results are consistent with the additive effects of genetic and postnatal influences. Specific environmental influences implicated were multiple foster homes (for men) and extensive institutional care (for women).

29.6.2. Epidemiologic Studies—Family Studies

Of 223 male criminals, 80% were found to have a diagnosis of AP (181). Sixteen percent of the interviewed male first-degree relatives also had this diagnosis, while only 2% of female relatives had AP, compared to 3% and 1% in the relatives of controls. Increased rates of alcoholism and drug abuse were found among the first-degree relatives of these criminals.

A family study of 66 female felons and 228 of their first-degree relatives revealed increased rates for AP (18%), alcoholism (29%), drug abuse (3%), and hysteria (31%) with all of the hysteria occurring in the female relatives (182). Predictably, the male relatives had a three-fold increase in AP (31%) compared to the female relatives (11%). The increased risk for AP among first-degree relatives of female felons (31%) compared to the risk for relatives of male felons (16%) may be related to a greater genetic and social predisposition which may be present in the families of the female felons, yielding a higher risk in these relatives.

29.6.3. Cytogenetic Studies

Several reports have suggested that the prevalence of XYY males among the populations of prisons and penal/mental institutions is higher than the prevalence in the general population. The XYY karyotype is associated with slightly lower than normal intelligence, tall stature and cystic acne. This karyotype is found in approximately 1/1000 male newborns but Hook found XYY in 1/53 from 3813 males in 20 penal/mental institutions (422). Witkin et al. (183) surveyed all tall Danish men from a birth cohort, finding 12/4139 (0.29%) men who were XYY. Five of these 12 XYY men had some criminal record, primarily petty criminality. Witkin suggests that lower than average intelligence may account for the excess of criminal activity among XYY males. This karyotype does not seem to be associated with a predisposition to impulsive violence.

29.6.4. Biological Markers

Nielsen (184) identified a variant of the tryptophan hydroxylase gene (which codes for the synthetic enzyme for serotonin) associated with low 5-hydroxyindoleacetic acid (5HIAA) in cerebrospinal fluid of violent criminal offenders who attempted suicide. However it was subsequently found that this variant (TH1) is much less important than its isoform (TH2) for central nervous system serotonin levels. This area is still under investigation (185). Low 5HIAA has been associated with impulsivity and violence in experimental colonies of rhesus monkeys (186, 187) as well as in man (188, 189). A Dutch family was reported with lowered monoamine oxidase A activity caused by a point mutation on the eighth exon of the MAOA gene. The males with this mutation (both MAO genes are on the X chromosome) showed impulsive aggression, arson, attempted rape, and exhibitionism (190). It seems likely that other familial monoamine defects may be found to be associated with aggressive behavior.

29.7. Anxiety Disorders

Observations on the increased familial risk for anxiety disorders have been recorded in the literature for over 100 years. Family studies of Panic Disorder (PD) using modern criteria are often complicated by comorbidity with Social Phobic Disorder and Generalized Anxiety Disorder. One family study of pure panic disorder probands found a significantly higher risk for panic among first-degree relatives compared to relatives of controls (191). There was also a five-fold increase in risk for any anxiety disorder. Similarly, an increased (11.6%) risk for agoraphobia has been reported for the relatives of agoraphobic probands, compared to 1.9% for relatives of panic probands and 1.5% for control probands. A study of simple phobia (192) found an increased risk (31%) for simple phobia among relatives of probands with that diagnosis (but no other anxiety disorder) compared to relatives of well probands (11%). A family history study of social phobia (193) demonstrated that relatives of phobic

probands were at increased risk for this disorder (6.6%) compared to relatives of panic disorder probands (0.4%) or relatives of controls (2.2%).

Distinctly separate genetic transmission for generalized anxiety disorder is not well established. In a family study, Noyes et al. (194) found that relatives of probands had a greater risk than relatives of controls, but this risk was not greater than the risk for relatives of panic disorder probands. Conversely, a separate study reported similar risks for generalized anxiety among relatives of panic disorder probands and relatives of probands with generalized anxiety. Thus, while there is some evidence for familial transmission of generalized anxiety, the transmission may not be specific.

In summary, family studies provide evidence that some anxiety disorders may be transmitted separately from one another. This is best established for panic disorder and least so for generalized anxiety.

29.7.1. Twin Studies

In a Norwegian sample (195), the concordance of all anxiety disorders for MZ twins (34.4%) was significantly greater than that for DZ twins (17.0%). More recently, in an Australian population sample of 5,440 twin pairs and 1,245 single twins, there was evidence for shared risk of major depressive disorder, panic disorder, generalized anxiety disorder and social phobia (196). Thus, current definitions of anxiety disorder subtypes do not create biologically distinct entities.

29.7.2. Linkage Studies

Crowe has studied 26 families with multiple cases of PD, including 198 informative persons, 39% of whom have definite or probably PD (197). Hamilton and colleagues (198) reported a syndrome linked to chromosome 13q; the complex phenotype included anxiety disorders and urinary tract dysfunction.

29.7.3. Association Studies

GWAS analysis of anxiety disorders has yielded evidence that TMEM132D alleles increase risk for anxiety disorders (199). TMEM132D is a single-pass transmembrane protein with a poorly understood function in the CNS. A two SNP haplotype (rs7309727 and rs11060369) located in intron 3 of TMEM132D is associated with a spectrum of anxiety disorders, most prominently panic disorder.

29.8. Attention Deficit Disorder

Early family studies of Attention Deficit Disorder noted alcoholism and sociopathy in male relatives and hysteria in female relatives (200). This same constellation was not manifest in the adoptive parents of adopted ADD children (201).

Family studies suggest that antisocial personality aggregates in the relatives of ADD children, specifically when the probands have had conduct or oppositional disorder (202). Biederman and colleagues found rates of Mood illness increased in relatives of their group as well. ADD itself was also increased in relatives and ADD and antisocial behavior tended to occur together.

Hauser et al. (203) reported mutations in the gene for the thyroid hormone receptor in one group of subjects with ADD (203). A family-based association study has implicated a gene for the dopamine transporter (204). The gene coding for the DRD4 receptor has been associated with ADHD in a meta-analysis (205). Genetic results have stimulated extensive investigations on the pathophysiology of attention deficit disorder in recent years, particularly related to the dopamine neurotransmission system.

29.8.1. Genomewide Association Studies

GWAS studies in ADHD have not yet tested samples of sufficient size to demonstrate consistent genomewide significant results.

29.9. Autism (Pervasive Developmental Disorder)

The pooled frequency of autism in sibs is about 3% (206), which is 50–100 times the population rate. Folstein and Rutter (207) reported an MZ concordance of 36% and a DZ concordance of 0%. When the phenotype was extended to include language and cognitive abnormalities, concordance rates were 82% and 10%. This sample of twins, though carefully selected, was small (N = 21) but the essential conclusions regarding heritability have been borne out in studies by Le Couteur et al. (208) and Steffenburg et al. (209).

A segregation analysis in a series of multiplex families was consistent with autosomal recessive inheritance though the excess of affected males in the sample suggests sex-specific modifying factors (210). What is perhaps more striking about the known genetics of autism is the association of multiple single-gene disorders with the syndrome. The most clearly documented of these disorders is the Fragile X syndrome; perhaps 8% of autistic subjects have the cytogenetic Fragile X and 16% of Fragile X males are autistic (211). However studies in a series of families did not provide evidence for a major role of fragile X mutations in autism (212). There are also probable associations with tuberous sclerosis, neurofibromatosis, and phenylketonuria. A variety of other reports of chromosomal anomalies and single-gene associations with the autistic syndrome have been summarized by Reiss et al. (213). Thus a variety of different single-gene abnormalities may serve as the first step in the pathophysiology of the autistic syndrome.

A number of genome-wide genetic surveys of the autistic phenotype have been reported. All of these studies have examined affected pairs of siblings where both twins have a narrowly-defined phenotype of autism or where one sib has the narrowly-defined autistic phenotype and the other has a defined pervasive developmental disorder. A consistent finding is seen on the long arm of chromosome 7 from 7q22-qter (214) (IMGSAC) (215–217). This region has been designated AUTS1 and stretches from genetic marker D7S524 (104.86 cM) to D7S483 (176.48 cM). The highest non-parametric multipoint MLS score achieved in one analysis was 3.2 at D7S477 (119.6 cM) (217) and a LOD = 3.6 at D7S530 (145 cM) was seen in another study (215). Folstein (218) reported that the linkage on 7q was specific to families in which the proband had a specific language disorder (usually reading difficulty along with later onset autism). It is notable that the linked region includes the gene recently dubbed ‘speech 1’ (also known as FOXP2 and demonstrated to be a transcription factor), which was recently found to be associated with a specific language disorder.

A significant finding has been found on chromosome 2q32 at D2S2188 (206.39 cM) with a multipoint MLS of 3.74 (216). This region is weakly supported by an earlier study by Philippe et al. (219). Other statistically suggestive regions found to date are on chromosomes: 5q14, 13q21, 16p13.3 and near the centromere of chromosome 19.

The presence of an autistic phenotype in individuals having chromosomal duplications associated with Prader-Willi/Angelman syndrome on 15q11-q13 has focused considerable research in this region of the genome. The region of interest has focused around the GABRB3 receptor gene in 15q12. GABRB3 shows peak expression both temporally and spatially during pre- and early post-natal murine brain development.

Due to the finding of hyperserotonemia in a proportion of autistic children, it has been suggested that the serotonergic system may play an important role in the etiology of the disease. There are conflicting results regarding the genetic involvement of SLC6A4. Recent summaries of the genetics of autism show a striking combination of rare alleles, common alleles, and cytogenetic abnormalities thus far identified (220, 221). Candidate gene studies have implicated the serotonin transporter, reelin, and the neuroligins as possible single genes associated with the autism spectrum.

29.9.1. Candidate Gene Studies of Autism

What is the value of candidate gene studies? It is reasonable to question the value of candidate gene studies given that genome-wide searches for statistically acceptable candidates in autism have not yet been clearly productive. This suggests that common variants conferring a relative risk of ~1.5 or more are not likely. However candidates may still be important given a variety of scenarios: 1) common variants of small effect seem likely (222), and may explain a substantial portion of the variance (~40%) in the population distribution of ASD (223); 2) rare candidates of large effect may be present, and may be critically important in certain families, and 3) candidate genes may be strongly associated with subsets of ASD subjects defined by clinical, neurobiological, or family characteristics. It is important to note also, that the significance of individual candidates may go beyond their association with illness in certain families or groups. Candidates may be a window into neurobiologic processes of more general salience for autism and related disorders.

What is the genetic association evidence for specific candidates? Neuroligins, Neurexins, SHANK, CNTNAP– These are cell adhesion proteins involved with synapse formation, structure, and activity (224). 47 variants have been described in ASD subjects in the literature; similar variants are quite rare in controls. There are some issues with non-penetrance within pedigrees and with phenotypic heterogeneity (alternate phenotypes ID or SZ).

SLC6A4—the serotonin transporter. A classic candidate for autism because of abnormalities such as low blood serotonin in subjects with autism. Meta-analyses are substantially negative (225, 226). However, there is some evidence for rare variants.

MET—Proto-oncogene. This is a receptor for hepatocyte growth factor and a tyrosine kinase. A knockout mouse model exists. Three allelic variants are associated with autism as well as two CNVs (227).

MECP2 (methyl CPG-binding protein 2); a transcriptional regulator localized to chromosome X; this gene is the cause of Rett syndrome, which is, broadly, an ASD that includes specific motor dysfunction. A mouse model of this condition exists. MECP2 duplication syndrome appears to be associated with autism, at least in males (228).

OXTR and AVPR1a—indirect and suggestive evidence for association (229)

RELN—The association evidence is ambiguous for this plausible candidate gene involved in neuronal migration (423).

FOXP1 and FOXP2—These genes appear to be associated with language dysfunction in autism and other disorders (424)

GABRB3—Association with GABRB3 has been reported in several studies in independent samples (230).

EN2—engrailed homeobox 2. This is a positional candidate (that is, it is located near a linkage peak) with evidence in several cohorts (231).

What about candidates associated with specific genetic syndromes? There are over one hundred single-gene syndromes that may be associated with autism/ASD features (232). Examples of genes regarded as candidates for this reason would include FMR1 and MECP2.

Summary

The strongest candidate gene evidence is for genes coding for cell adhesion proteins (e.g., *neuroligins, neurexins, SHANK, and CNTNAP*). Evidence is also substantial for *GABRB3, EN2, and MET*. In general, estimates of the quantitative contribution of specific candidates to autism genetics will require full genomic investigation of large samples of cases and controls.

29.9.2. Genome-Wide Association Studies of Autism

29.9.2.1. Genome-Wide Association Study Results in Autism Spectrum Disorders

GWAS results in autism spectrum disorders have so far been equivocal. Wang et al. (233), studied 780 families, including 3101 subjects; they also included 1204 cases and 6491 controls. Subjects were genotyped on the Illumina 550 platform. A replication sample included 447 families with 1390 subjects, as well as 108 cases and 540 controls. A locus was identified at 5p14.1 between CDH9 and CDH 10 at a p value of 3.4×10^{-8} . The evidence became stronger with the replication sample. Weiss et al. (234) studied two samples, one with 780 families including 3000 subjects and one with 341 families including 1243 subjects; replication samples included 315 trios and 1755 trios. Genotyping was performed on the Affymetrix 5.0 array: a locus was identified at 5p15.2 between SEMA5A and TAS2R1, and this was found to be genome-wide significant using permutation analysis with $p < 2.5 \times 10^{-7}$. Anney et al. (235), reported AGP data from 1365 families (1389 probands) on the Illumina 1 M platform, then ran a mega-analysis on 2179 families and 1849 controls: they reported a p value of 3.7×10^{-8} for MACROD2 at 20p12.1 Devlin et al. (222) shows that the Wang, Weiss, and Anney studies do not replicate each other and that sample sizes of ~ 7–10,000 are likely to be needed to achieve replicable results for autism since the odds ratio at any one locus is likely to be <1.5 for the risk allele compared to the non-risk allele. The current sample available for analysis in the Psychiatric GWAS Consortium includes 4788 trios along with 161 cases and 526 controls (from PGC Cross-Disorders Group, unpublished data).

29.9.3. Copy Number Variant Studies of Autism

Sebat et al. (236) reported de novo copy number variants in 7% of subjects with autism compared to 1% of controls. When he divided subjects into simplex or multiplex, the simplex subjects had a 10% rate of CNVs. Pinto et al. (23) found that the difference between cases and controls was particularly striking when considering CNVs that disrupted genes implicated in autism and intellectual disability on the basis of cytogenetic reports. Malhotra and Sebat (237) summarized this area, implicating regions on chromosomes 1, 7, 15, 16, 17, and 22 (425).

29.9.4. Sequencing Studies of Autism

The Autism Sequencing Consortium (238) has been formed to support studies of sequence variants in autism and autism spectrum disorders. Most of the work so far has been on the exome. Initial data has identified a number of de novo loss of function variants (239–241). A recent whole genome study identified deleterious de novo mutations in several autism candidate risk genes (242).

29.10. Drug Abuse

Cadoret et al. (127) reports an adoption study of drug abuse. 443 adoptees from Iowa were studied; half were selected for psychopathology in biologic parents and the other half matched for age and sex. Parents were not directly examined but information from adoption records was available. Forty adoptees manifested drug abuse of one kind or another. Antisocial behavior in a biologic relative predicted drug abuse in the adoptee and alcohol problems also predicted abuse in the absence of antisocial behavior. Environmental factors implicated included divorce and significant psychiatric pathology in the adoptive parents.

Grove et al. (243) report a study from the Minnesota sample of 32 MZ twins raised apart. Significant heritability was shown for drug abuse or dependence. Probandwise concordance was 36%. Concordance in this range suggests a combination of genetic and environmental effects.

Mirin et al. (244) reported considerable comorbidity for alcoholism and other Axis I disorders in substance abusers and a relationship between the type of comorbid disorder (alcoholism or Mood disorder) in probands and the rate of that same disorder in relatives. Rounsaville et al. (245) reported significantly increased risk for substance abuse, alcoholism, antisocial personality, and major depression among the relatives of opiate dependent probands compared to controls.

Berrettini and colleagues studied variants of the mu opiate receptor gene in a mouse model as well as in humans with opiate abuse. Variants are associated with differences in promoter activity in mice (246). In man, variants in the mu receptor gene do not appear to be associated with opiate dependence but are associated with response to naltrexone among alcohol dependent patients (247) and with response to nicotine replacement therapy among smokers (248). The NIDA Genetics Consortium has supported numerous genetic studies of substance abuse in the past few years, and important results are now starting to emerge. One of the first genome-wide association studies was performed in subjects with nicotine dependence, as part of this consortium. Recent results suggest that multiple loci among genes coding for nicotine receptor subunits are pertinent to pharmacologic response to nicotine and subsequent dependence (249).

29.11. Eating Disorders

29.11.1. Family Studies

Controlled family studies have been conducted over the past two decades. These studies suggest that there is considerable familial aggregation. It is difficult to estimate precisely the risk to first-degree relatives because the control samples are not sufficiently large to detect more than 1–2 affected relatives of controls. However, the overall pattern suggests substantial risk, almost certainly greater than RR =10 and perhaps much larger. There are increased rates of AN among first-degree relatives of probands, and increased rates of BN among first-degree relatives of AN probands. This clustering of eating disorders in families of AN and BN individuals provides strong support for familial transmission of both disorders.

29.11.2. Twin Studies

There have been a number of twin studies of AN. However, many of the studies were small and often had methodological weaknesses (419). If one examines the twin studies with the largest number of subjects and most appropriate methodology (250, 251) mean concordance rates are 64% for MZ twins and 14% for DZ twins. Differences between these rates suggest a modest additive heritability with a large influence of non-additive genetic and/or shared environmental factors. More recent studies have used structural models to estimate the fraction of risk attributable to additive genetic factors. The estimates of heritability range from 0.48 to 0.76.

Holland et al. (250) report pairwise concordance of 56% in MZ and 5% in DZ pairs (71% and 10% with probandwise figures). Family history assessment (including additional informant data from parents) showed that 4.9% of the female first-degree relatives and 1.16% of the female second-degree relatives had had anorexia at some point in their lives, a risk considerably higher than the reported population prevalence. The MZ cotwins were much more similar in "body dissatisfaction," "drive to thinness," weight loss, length of amenorrhea, and minimum body mass index. Estimates indicate that roughly 58–76% of the variance in the liability to AN (252), and 54–83% of the variance in the liability to BN (253, 254) can be accounted for by genetic factors. Although the confidence intervals on these estimates are wide, consistent findings across studies support moderate heritability of these traits (255). For both AN and BN, the remaining variance in liability appears to be due to unique environmental factors (i.e., factors that are unique to siblings in the same family) rather than shared or common environmental factors (i.e., factors that are shared by siblings in the same family).

Eating disorder symptoms themselves also appear to be moderately heritable. Twin studies of binge eating, self-induced vomiting, and dietary restraint suggest that these behaviors are roughly 46–72% heritable (256, 257). Likewise, pathological

attitudes such as body dissatisfaction, eating and weight concerns, and weight preoccupation show heritabilities of roughly 32–72% (257–260). Taken together, findings suggest a significant genetic component to AN and BN as well as the attitudes and behaviors that contribute to, and correlate with, clinical eating pathology.

29.11.3. Molecular Studies

The first AN linkage scan was based on ~ 200 multiplex kindreds and revealed a locus on 1p (NPL score = 3.5 at D1S3721, 72.6 cM (261). Additional genotyping in the region resulted in an increased NPL score of 3.91 at 72.0 cM (262). Analysis of diagnostic phenotypes, using obsession scale scores and drive for thinness scores as covariates, revealed additional linkage peaks (263). SNP genotyping at several candidate genes (HTR1D, HCRTR1, and OPRD1) revealed limited evidence for association with the HTR1D and OPRD1 genes. These observations were confirmed in an independent population of AN individuals (264).

The first BN linkage scan was based on ~ 300 multiplex families and yielded a genome-wide significant LOD score of 2.92 on chromosome 10 p. When analysis was restricted to those ~ 133 multiplex kindreds characterized by self-induced vomiting, the LOD score on 10 p increased to 3.39. A promising candidate gene within the 10p linkage peak is glutamic acid decarboxylase (GAD2), a gene implicated in obesity (265).

Many family-based and case-control association studies of monoamine-related, obesity-related and neurotrophin-related genes have been published in the past 10 years. These have been small, underpowered and limited in the numbers of genes (and variants within genes) tested (253). More recently larger samples sizes have been employed in candidate gene studies, using collaborative, multi-site approaches. For example, Ribases (266) reported that the Met allele of a missense variation in the BDNF gene was associated with AN in Spanish patients. Subsequently, this was confirmed (267, 268) in European collaborative samples totaling greater than 1500 patients.

A GWAS of 1000 AN cases and 4000 control women did not yield any genome-wide significant result (269). Despite the relatively uniform phenotypic presentation of AN, it seems to be as genetically complex as other psychiatric disorders, with no common alleles of even moderate effect sizes.

29.12. Intellectual Disability

29.12.1. Epidemiologic Studies

Twin studies (performed 40–60 years ago) show an MZ concordance of 100% (N = 83) and a DZ concordance of 55% (N = 10). These would undoubtedly be performed today with separation according to specific causal factors. Adoption studies have not been performed.

Recurrence risk for siblings of a child with intellectual disability (ID) has been estimated to range from 9.5% to 23% depending on severity of the disorder and the mother's reproductive history (270). For mothers who have already had more than one child with ID, the risk is 25–50% for sibs.

29.12.2. Specific Etiologic Causes

Many medical syndromes are manifest as ID, such as specific errors of metabolism and chromosomal anomalies (271, 272). Polani (273) estimates that 4% of human conceptions are chromosomally abnormal but that 85–90% of these are selectively eliminated as spontaneous abortions. Of live births, 6% may have a genetic or developmental abnormality of some type, including 0.5% surviving with chromosomal abnormality, 4% with another developmental anomaly, and 1.5% with a single gene disorder of some type. Among single gene causes of ID, Koranyi lists five dominant diseases (tuberous sclerosis, neurofibromatosis, Sturge-Weber disease, von Hippel-Lindow, and craniosynostosis), and four recessive (Hurler-Hunter disease, galactosemia, G-6 phosphodehydrogenase deficiency and familial hypoglycemia), as well as three recessive aminoacidurias, and three lipid-related disorders. Many more are listed in McKusick's compendium (MIM).

If we consider disorders causing ID according to their frequency in the population, we may see the following:

Down's syndrome accounts for ID in 1.5 persons per 1,000 and is the most common single cause of the condition (274). The prevalence of Downs varies greatly and is primarily determined by maternal age. Familial microcephaly is present in about 1/40,000 births but may account for a significant proportion of ID because of effects in heterozygotes (see below). Fragile X

syndrome accounts for about 0.5/1,000 and other X chromosome syndromes for another 1/1,000. All metabolic causes together are responsible for 1/1,000 and chromosomal abnormalities for 3/1,000.

29.12.2.1. Down's Syndrome

This condition, well studied, is accounted for by a triplication of genetic material on a portion of chromosome 21. The area is being localized more and more precisely using molecular techniques combined with cytogenetics (275, 276). It is probable that sections of 21q22.2 and 21q22.3 are involved, though some work implicates 21q21 (277). The areas implicated include genes for amyloid and superoxide dismutase. The ETS-2 proto oncogene is near this area as well, and its presence may be related to the well described increased incidence of leukemia in persons with Down's syndrome and their relatives (278–280). Human 21q21-22.3 is homologous to portions of mouse chromosome 16. A mouse model of Down's has been described based on a laboratory-generated reciprocal translocation involving this area (281, 282).

The reasons for triplication or nondisjunction in Down's are not entirely clear. The likely etiologic factors are environmental rather than genetic and vulnerability for the condition does not seem to be inherited. A small proportion of Down's patients have a translocation rather than a triplication (283).

As noted above, the clearest correlate is maternal age. Yet it has been known for some years that the origin of the nondisjunction may be paternal as well as maternal (284). Serum markers may now contribute to prenatal determination (decreased alpha-fetoprotein and estriol and increased human chorionic gonadotropin), and may aid in the selection of women for referral to amniocentesis (285).

It has been reported (280) that a familial association exists between Alzheimer's and Down's, but this is unlikely to be generally true (286). Recent studies suggest that triplication of a critical region on chromosome 21 is not likely to be the sole cause of clinical variation in Down's Syndrome, and that other genomic areas are probably important as well (287).

29.12.2.2. Fragile X

Fragile X syndrome is named after a cytogenetic observation; cultured cells from some patients show chromosomal breakage under appropriate conditions. There are actually multiple "fragile sites" on human chromosomes (288). The fragile X (breakage at Xq27.3) is merely the best known. The syndrome itself was originally described by Martin and Bell (289); who described a large pedigree with ID segregating in an X-linked recessive pattern.

Fragile X is the most common form of X-linked ID and is, in general, the most common heritable form of ID (Down's being genetic but not inherited). It is estimated that 1/850 persons carry the defect. Of those, 4 out of 5 males will express the clinical phenotype as compared with 1 out of 3 females (thus some homozygotes are non-penetrant and some heterozygotes are penetrant). RFLP tests are now available to determine carrier status in non-penetrant individuals; the error rate should now be 5% or under with available probes and new polymorphisms are being developed at a rapid rate (290, 291). The precise genetic error in the Xq27.3 region is now known to be a triplet repeat of variable length. Increased numbers of repeats (associated with greater severity of illness) are seen as the gene is passed to succeeding generations. When the number of repeats exceeds a threshold, clinical manifestations are seen.

Most female heterozygotes do not have ID. However Reiss et al. (292) have demonstrated schizotypal features in about 1/3 of a sample of carriers, as well as a weaker association with chronic or intermittent Mood disorders. Several studies have suggested a connection with autism (293, 212). Mendlewicz & Hirsch (294) described a family in which Fragile X syndrome segregated with manic depressive illness and where data are consistent with linkage to the Xq27 area.

Clinical genetic studies of Fragile X and similar conditions associated with fragile sites were summarized by Sutherland and Baker (295). Raymond and Tarpey (296) have reviewed the general area of genetic causes of ID (formerly termed mental retardation).

29.13. Obsessive–Compulsive Disorder

29.13.1. Epidemiologic Research—Twin and Family Studies

There are no large twin studies of OCD. Rasmussen and Tsuang (297) reviewed reported series and noted that 32 of 51 (63%) MZ pairs were concordant. However, assignment of diagnosis and zygosity has been questioned in some of these cases (298). There is general agreement on 13 concordant MZ twin pairs and 7 discordant MZ twin pairs. There are several unquestioned reports of discordant MZ twin pairs for OCD, implying some nongenetic factors in incidence or age of onset.

Lenane et al. (299) studied 145 first-degree relatives of 46 children with OCD. Of the 90 parents personally evaluated, 15 (17%) received a diagnosis of OCD, compared to 1.5% of the parents of 34 conduct-disordered children who served as a control

group. This 17% rate is also significantly higher than the population prevalence rate of 2% (300). Fathers were 3 times as likely as mothers to receive a diagnosis of OCD. Of the 56 siblings personally evaluated, three (5%) met criteria for OCD. When age-correction was applied, this rate was 35%. This figure should be viewed with caution because of the magnitude of the age correction for siblings. It should be noted that the probands all had severe childhood-onset OCD, and were referred to the authors for treatment protocols. It is possible that childhood-onset OCD represents a more severe form of the OCD spectrum. Nevertheless, this carefully conducted family study reveals an increased risk for OCD among the first-degree relatives of OCD probands.

29.13.2. Spectrum

When OCD occurs in the familial context of Tourette's Syndrome, the OCD may be considered part of the spectrum of Tourette's Syndrome. However, most OCD occurs in individuals who have no first-degree relatives affected by Tourette's Syndrome. Occasionally, an individual destined to develop Tourette's Syndrome will present with symptoms of OCD, and the motor tics appear subsequently. These patients are often diagnosed as having OCD until the motor tics develop.

There is limited evidence from family, twin and adoption studies, regarding the inheritance of OCD. Although OCD may be familial, there are insufficient data from twin studies and no data from adoption studies. Several avenues of research suggest a serotonergic abnormality for OCD patients. Recent data from Goldman shows a rare mutation in the serotonin transporter associated with obsessive-compulsive disorder in a single pedigree (301).

More recently, a GWAS study of 1465 persons with OCD and 5557 ancestry-matched controls was published (302). No locus reached genome-wide significance, indicating that there are no common alleles conveying even moderate levels of risk for OCD.

29.14. Schizophrenia

29.14.1. Twin Studies

Twin studies of schizophrenia were summarized by Nurnberger et al. (303). Several conclusions were drawn from these data. First, monozygotic twin concordance is greater than dizygotic twin concordance within each study, which is consistent with genetic hypotheses (the average was 49% in MZ twins and 9% in DZ twins, using a broad phenotype definition). Second, the heritability of broadly defined schizophrenia (44%) is greater than the heritability of strictly defined schizophrenia (27%). This is consistent with a spectrum concept; i.e., some individuals with the genetic loading for schizophrenia manifest a somewhat different condition, such as schizotypal personality disorder or paranoid personality disorder. Third, the amount of discordance is considerable; even in MZ twins using a broad definition of illness the total discordance was 51%. Sullivan et al. (304) reported a meta-analysis of 12 twin studies; showing a heritability estimate of 81% (confidence interval 73%–90%), but also an environmental component accounting for 11% of the variance (3%–19%). It was suggested that intrauterine factors might be important environmental influences, and this is consistent with epidemiologic studies (305) and investigations of viral etiology (306, 307).

Inouye (308) reported on a series of 9 monozygotic twins with schizophrenia who were raised apart from infancy. Three were regarded as completely concordant and three were partially concordant.

Abe (309) utilized a twin study paradigm to generate data regarding environmental effects in schizophrenia. Examining age of onset in the Maudsley Hospital twin series, he found that there was a high incidence of illness in the second of a pair of twins within two years of the onset in the first twin. Further categorizing the group on the basis of whether the twins lived together or lived apart, he found the excess to be primarily in those living together. That is twins living together show concordance in age of onset, while twins living apart do not. This is an intriguing finding suggesting an environmental factor.

29.14.2. Family Studies

The pooled European family study data show an age-corrected morbid risk of 5.6% in parents, 10.1% in siblings, and 12.8% in children (310). It is thought that the lower rate in parents is related to a relative decrease in fertility among schizophrenic patients. General population figures for morbid risk for schizophrenia range around 1%, and thus all classes of first-degree relatives have a clear increase in prevalence. The risk for offspring of two schizophrenic parents is difficult to estimate because of the small number of cases, but probably runs between 35% and 45% (in the pooled data it is 46.3%). Among second-degree relatives (uncles, aunts, nephews, nieces, grandchildren), half-siblings, and cousins, the risk ranges from 2–4%.

Thus, close relatives of schizophrenic patients suffer about a 5 to 10-fold excess risk for the illness, and that the risk diminishes in more distant relatives. An additional group of first-degree relatives appear to develop "spectrum" disorders (see below). However, the majority of close relatives of schizophrenics are psychiatrically normal.

It is hard to make a strong case for genetic determination of the classical subtypes of schizophrenia (Kraepelin's hebephrenic, catatonic, and paranoid forms). Though there is significant concordance in monozygotic twins for subtype (310), this does not hold true in family studies (311).

The question of the distinctness of schizophrenia and Mood disorders is not easily settled. In a large family study using lifetime diagnoses and separately examining relatives of probands with schizophrenia, chronic schizoaffective disorder, acute schizoaffective disorder, bipolar affective disorder, unipolar depression, and controls, Gershon et al. (75) concluded that there was evidence for overlap in genetic liability. Specifically, an increase in unipolar disorder was seen in all groups of relatives of patients, and relatives of schizoaffective probands (both chronic and acute) showed both an excess of Mood disorders and an excess of chronic psychoses. However, bipolar probands did not show an excess of schizophrenic relatives, nor did schizophrenic probands show an excess of bipolar relatives. The most parsimonious explanation of these data is that there is a "middle" group of disorders (schizoaffective) that is genetically related to both schizophrenia and Mood disorders, and that it may not be possible at this time to completely separate the groups on clinical criteria.

With regard to mode of transmission, the available data have been analyzed extensively; results have generally been interpreted as favoring a multifactorial rather than a single-locus model (312, 313).

29.14.3. Adoption Studies

The adoption study methodology was first applied to schizophrenia by Heston (314), who found more schizophrenia in the adopted-way offspring of schizophrenic women than in control adoptees. A series of large, systematic studies were carried out by Kety et al. (315–317) and Rosenthal et al. (318), who made use of adoption and psychiatric hospitalization registries in Denmark. In the later studies, subjects were directly interviewed. In all studies, adoptees were separated from their biologic parents at an early age and adopted by non-relatives. It was found that there were more schizophrenia and schizophrenia spectrum disorders in the biologic relatives of schizophrenic adoptees than in the biologic relatives of psychiatrically normal adoptees. The prevalences of psychiatric illnesses in the adoptive relatives of the two groups were small and comparable.

Rosenthal et al. (318) also found the frequency of schizophrenia spectrum disorders to be higher in adopted-away offspring of schizophrenic parents than in the adopted-away offspring of normal parents. All of these studies have been criticized for the selection of subjects, validity of diagnoses, and validity of comparisons (319, 320). However, further independent analysis of the data has confirmed the essential results: that is, biologic relatives of schizophrenics who have not shared the same environment have a significantly higher prevalence of schizophrenia and schizophrenic spectrum disorders than do biologic relatives of comparable control groups (321, 322).

29.14.4. Spectrum

Several investigations in this area have been performed by Baron and coworkers (323). They have reported that up to 30% of first-degree relatives of schizophrenic patients have associated disorders. The particular DSM-III-R diagnostic categories that seem to be implicated are paranoid personality and schizotypal personality. Tsuang et al. (324) have argued that the evidence for schizotypal personality disorder being part of the schizophrenia spectrum is strong, with suggestive evidence for paranoid and schizoid as well. Kendler (325–327) has argued for a separate entity characterized by paranoid delusions only (simple delusional disorder) with inheritance independent of schizophrenia and mood disorders.

29.14.5. Molecular Studies

Multiple linkage scans of the genome have been conducted with a diagnostic phenotype of schizophrenia, using DSM-III, DSM-IV, IDC and/or RDC criteria. These linkage scans have been the subject of meta-analyses (328, 329), in which available data have been combined using different methods, and results are only partially convergent. Genomic regions implicated in these meta-analyses include 1q, 5q, 6p, 6q, 8p, 13q, 15q and 22q. Several of these regions will be discussed below, with a focus on those with highly promising candidate genes.

On chromosome 6p, Straub et al. (330) first published evidence that the dysbindin (DTNBP1) gene showed association with schizophrenia. Multiple confirmations followed (331–334), although some negative reports exist (335). Multiple haplotypes have been associated with schizophrenia in these reports. There is evidence that dysbindin levels are reduced in post-mortem schizophrenia brains (336–338). A SNP in the 3'UTR of the dysbindin gene may mediate the reduced expression (337, 338). At

least one dysbindin risk haplotype may be associated with decreased cognitive ability (339). There may be some overlap between psychotic bipolar disorder and schizophrenia in terms of dysbindin risk alleles (340).

An 8p candidate gene, neuregulin 1 (NRG1), was associated with SZ (341–348). While there is substantial genetic evidence for a NRG1 role in the genetics of SZ, other investigators (some employing multiplex samples with positive linkage signals in the region) could not confirm the NRG1 association with SZ (349–354). Interestingly, Green et al. (355) found evidence for association of NRG1 alleles with psychotic bipolar disorder, suggesting some genetic overlap between this entity and schizophrenia.

Chumakov et al. (356) found association to schizophrenia in French Canadian and Russian populations at two novel genes, G72 and G30, which are overlapping and oriented in opposite directions on 13q33. G72 is a primate-specific gene possibly expressed in the caudate and amygdala, although some authorities have not been able to detect mRNA in post-mortem human brain. Using yeast two-hybrid analysis, evidence for physical interaction was found for G72 and D-amino-acid oxidase (DAO). DAO oxidizes D-serine, a glutamate receptor modulator. Co-incubation of G72 and DAO in vitro revealed a functional interaction with G72 enhancing the activity of DAO, such that G72 has been named D-amino-acid oxidase activator (DAOA). Associations between DAOA and schizophrenia have been reported in samples from China (357), Germany (358), Ashkenazis (359), South Africa and the US (360). Childhood-onset schizophrenia has also been associated with DAOA in a small sample (361). Various risk alleles and haplotypes have been reported in schizophrenia. Curiously, multiple independent datasets suggest that this locus contributes to risk for bipolar disorder (84, 83–86). No clear functional variation has been found.

There are several other candidate genes which have been implicated repeatedly in the etiology of schizophrenia, including RGS4 (361), COMT (362, 363) and DISC1 (91).

29.14.6. Genome-Wide Association Studies in Schizophrenia

The field of schizophrenia genetics has been more strongly affected by GWAS studies than any other area of psychiatry. In 2009 the International Schizophrenia Consortium demonstrated clearly that the HLA region showed substantial association with schizophrenia. Since then substantial evidence has been accumulated for many candidate genes including the zinc finger protein gene ZNF804A, the microRNA mir137, and the transcription factor gene TCF 4. The sample size for schizophrenia GWAS studies is now >36,000 cases. During the last World Congress of Psychiatric Genetics, an illustration of 62 independent genome-wide signals was shown, and the number has increased since that time. The detailed publication of these results is presently awaited.

29.14.7. Endophenotypes in Schizophrenia

The concept of endophenotypes in psychiatric disorders has been developed over the last several decades. Gottesman and Shields (364) used the term, endophenotype, to define an illness-related characteristic, observable through biochemical testing or microscopic examination. It is assumed that a valid and useful endophenotype is more closely related to one or more pathophysiologic genes for the nosologic category, compared to the entire spectrum of disorders included in the nosologic category.

The utility of endophenotypes in psychiatric research is now more appreciated, because we have a more accurate understanding of the genetic complexity of operationally-defined disorders in our current psychiatric nosology. Endophenotypes should be valid approaches to creating more homogeneous subtypes of disorders, categories which may cut across the current nosologic boundaries. If endophenotypes can create more homogeneous subgroups of the traditional nosology of schizophrenia and mood disorders, then more rapid advances in understanding these disorders at the genetic and molecular levels can be made.

29.14.7.1. Criteria for an Endophenotype

Criteria for an endophenotype have been derived from those proposed by Gershon and Goldin (365):

1. The endophenotype must be associated with illness in the general population;
2. The endophenotype should be a stable, state-independent characteristic (that is, it must be observable despite the fact that the patient may be in partial or complete remission);
3. The endophenotype should be heritable;
4. The endophenotype should segregate with illness within families;

5. Among kindreds in which the proband has the endophenotype, the endophenotype should be observable at a higher rate among unaffected family members, compared to the general population.

Below, examples of promising endophenotypes in schizophrenia are summarized.

There are many reports of attentional deficit measures in schizophrenia. An endophenotype which has been studied extensively in schizophrenia is "working memory." This term can be defined as the "holding of information in consciousness, in preparation for complex processing." Working memory can be assessed through multiple different mental tasks, such as N back, Wisconsin Card Sort and reverse digit span. Deficits in working memory have been described as an endophenotype for schizophrenia (366). The fraction of individuals with schizophrenia who are designated as having abnormal working memory varies with the tests employed, the clinical population studied and the definition of abnormal (e.g., 1.5 or 2 standard deviation units below the mean for controls). If consideration is given only to studies of large numbers of cases (~100) and controls, most reports describe 25–50% of persons with schizophrenia as falling in the variably-defined "deficit range" for working memory (367–371).

Several lines of evidence suggest that the working memory deficits are in part heritable. Twin studies of unaffected and discordant (for schizophrenia) monozygotic and dizygotic twin pairs indicate that genetic influences in the schizophrenia-related working memory deficits are prominent (372–374). In addition, multiple studies suggest that a small fraction of the variance in working memory scores is explained by a functional missense SNP (Val/Met) in the COMT gene (370, 375, 376), although this finding is not observed consistently (377, 378).

Working memory deficits are more common among the unaffected relatives (compared to controls) of schizophrenic individuals who have deficits themselves (379). The effect size for this observation is relatively small, such that substantial sample numbers are required to have adequate power. If only those studies which examined at minimum ~50 relatives ~50 controls are considered (379–383), then there is a preponderance of data suggesting that unaffected relatives (of schizophrenic individuals) have some of the neuropsychological deficits seen in affected persons. However, one must be concerned with a negative publication bias, and with the fact that a wide range of neuropsychological measures have been used, such as Wisconsin Card Sort, digit span, trailmaking, tests of verbal and spatial fluency, etc. The effect size is not large, as evidenced by the fact that multiple smaller studies have not found a significant difference between relatives of schizophrenic individuals and controls (384, 385).

The preponderance of data suggests that neuropsychological/cognitive deficits in schizophrenia are present more often among affected persons, compared to controls. There are data to indicate that the measures are heritable. Finally, most larger studies find that non-psychotic relatives of schizophrenic individuals score more poorly on various neuropsychological tests, compared to controls. Thus, various measures of cognitive function are valid endophenotypes for schizophrenia, based on the criteria noted above.

One promising endophenotype for schizophrenia is an abnormality of the P50 auditory evoked potential (386). The P50 wave is a positive deflection (recorded by scalp electrodes) occurring 50 milliseconds after an auditory stimulus, typically a single click. When two such clicks are presented, the second occurring ~200 milliseconds after the first, the amplitude of the P50 wave after the second click is reduced normally, in comparison to the amplitude of the wave after the first click (see Fig. 29.3 below). This is considered by some to be an electrophysiologic signature of sensory gating. In some individuals with schizophrenia, the amplitude of the P50 wave for the second click is similar to the amplitude after the first click, ie, there is no amplitude reduction, as shown above. This is interpreted as a failure of sensory gating.

The P50 abnormality is found more often among individuals with schizophrenia, compared to controls (387, 388), although this is not universally confirmed (389, 390). The P50 abnormality is found more frequently among the relatives of persons with schizophrenia, compared to controls (391, 392). It is a partially heritable characteristic, based on twin studies (393, 394). Heritability is also implied by the reports that DNA sequence polymorphisms in and near the alpha 7 nicotinic receptor subunit gene on chromosome 15 explain some of the variance in the P50 abnormality (395–397). The chromosome 15 location is a confirmed linkage region for schizophrenia (398, 399, 395), thereby lending added confidence to this line of investigation.

While there is ample evidence that the P50 is partially under genetic control (393, 394), there is also substantial evidence that P50 parameters are influenced by environmental forces. For example, smoking or administration of nicotine may "normalize" an abnormal P50 test (400, 401). The finding becomes more intriguing when it is recalled that as many as 80% of individuals with schizophrenia are daily smokers (402). Additionally, there is evidence that atypical antipsychotic medications can "normalize" abnormal P50 testing (403–406). These results indicate a critical point when considering endophenotypes: environmental influences must be considered, not only as sources of variance (e.g., experimental error, circadian variation, influence of personal habits such as nicotine and caffeine intake), but also as clues to mechanisms which may provide pathways from gene variants to endophenotypes, or from endophenotypes to key symptom clusters or subtypes of disorders.

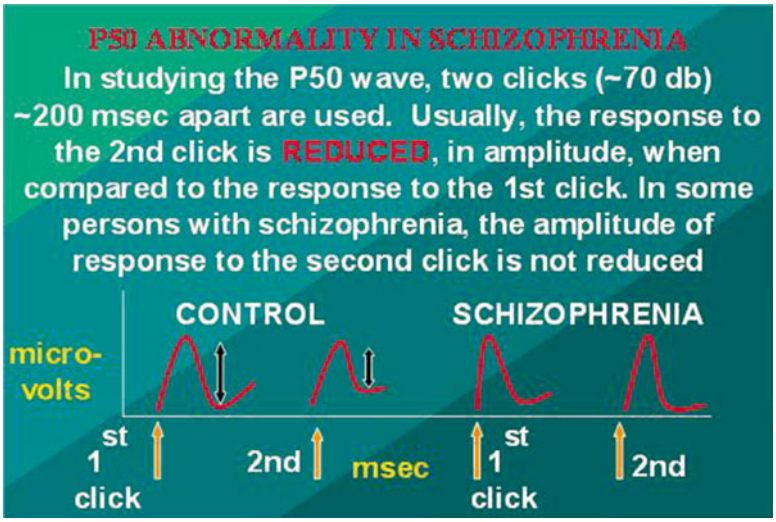

FIGURE 29.3 Diagram of a neurophysiological endophenotype in schizophrenia. The control subject shows decreased response to a second stimulus following soon after the first stimulus, but the subject with schizophrenia shows no such decrease. This is interpreted as a failure of *sensory gating* (387–397) and it appears to be a heritable characteristic related to schizophrenia.

In summary, schizophrenia genetic studies have identified numerous promising candidate genes through linkage and association approaches. These include DAOA, NRG1, dysbindin, DISC1, RGS4, COMT and others. Further, endophenotypic research has revealed several promising endophenotypes, including auditory evoked potential abnormalities and cognitive deficits.

29.15. Somatization Disorder

In a family history study, Coryell (407) evaluated first-degree relatives of 49 probands with Briquet's syndrome. The first-degree relatives of non-Briquet's syndrome hysteria and mood disorder probands formed the control groups. The risk for a complicated medical history was 8.0% (17/212) in the first-degree relatives of the Briquet's syndrome probands compared to control values of 2.3% (5/214) and 2.5% (7/283) ($p < .01$).

In a family study of Briquet's syndrome, Guze et al. (408) reported a significantly increased risk for Briquet's syndrome among the first-degree female relatives of Briquet's syndrome probands (7/105), compared to female relatives of control probands (13/532). Additionally, they reported an increased risk for antisocial personality among the male (18/96) and female (9/105) relatives of the Briquet's syndrome probands, compared to the risk for male (44/420) and female (14/532) relatives of controls.

Torgersen (409) studied 14 monozygotic twin pairs and 21 dizygotic twin pairs in which one member had a somatoform disorder (including somatization disorder, conversion disorder, psychogenic pain disorder and hypochondriasis). 29% of monozygotic twin pairs were concordant for some type of somatoform disorder compared to 10% of dizygotic twin pairs (not a significant difference in this small sample).

29.15.1. Adoption Studies

In an analysis of a large Swedish adoption cohort, Sigvardsson et al. (410) identified a set of discriminant function variables that distinguished female adoptees with repeated brief sick leaves for somatic complaints and psychiatric disability ("somatizers") from other female adoptees. In a subsequent analysis, Bohman et al. (116) divided these somatizers into two groups, high-frequency somatizers (those who have a high rate of psychiatric, abdominal, or back complaints) and diversiform somatizers (those who have a lower frequency of complaints, but with multiple and highly variable symptoms). Thirty percent of the high-frequency somatizers had histories of alcohol abuse and/or criminality (based upon the national registries for these behaviors). Their male biological relatives were at increased risk for violent criminal behavior and alcohol abuse. For both types of somatizers, a cross fostering analysis provided evidence for both congenital and postnatal influences on the development of the disorder. These studies suggest a familial connection between some types of somatoform disorder and alcoholism and criminality. This area was reviewed by Guze in (411) and by Torgersen in (412). Torgersen makes the appropriate point that not much research has been carried out in this area in the past two decades; the reason for this is not clear.

29.16. Tourette's Syndrome

29.16.1. Twin Studies

Price et al. (413) studied 43 pairs of same-sex twins, 30 MZ and 13 DZ pairs. MZ twin concordance was 77% for any tics, compared to 23% for DZ twins. For Tourettes per se, the MZ concordance rate was 53%, compared to the DZ rate of 8%. These are all significant differences.

Pauls et al. (414) studied 338 biological relatives of 38 Tourette's probands, 21 adoptive relatives and 22 relatives of normal controls. Among the biological relatives 8.3% (28/338) had Tourette's, while 16.3% (55/338) had chronic tics and 9.5% (32/338) had OCD. These risks are all significantly greater than the risks for the 43 relatives of controls.

Baron et al. (415) reported that the transmission of Tourette's and chronic tics was consistent with a single locus model. Kidd and Pauls (416) were unable to differentiate between a single locus model and polygenic models.

29.16.2. Linkage Studies

A collaborative effort to use systematic genomic screening to find genes causing Tourette's has been underway for several years. Recent results implicate chromosome 2p (417). Rare mutations in the dendritic growth protein SLITRK1 (chromosome 13q) have been associated with this condition (418).

29.17. Genetic Counseling

Genetic counseling of a patient with a psychiatric disorder involves advising the individual of the probability or risk that their offspring will develop the disorder. General population lifetime risk for unipolar illness (when defined to include incapacitation or severe impairment) is 8%. If an individual has a unipolar parent, his/her lifetime risk is double the general population risk, or 16%. Such individuals are also at four-fold increased risk for bipolar illness.

Some illnesses have fairly narrow age-at-onset distributions in the general population. For example, first episodes of bipolar illness almost always occur before age 50. Fully 50% of bipolar individuals develop an initial episode (either depressive or manic) prior to age 20. This should be considered in a general way when assessing risk. For example, an unaffected 40 year old child of a bipolar parent has already passed through most of the age at risk, and thus, his/her risk is substantially less than 9% to develop bipolar disease. An estimate of ~2% would be more accurate in this case. Similarly, for attention deficit disorder, onset is during childhood by definition.

This subject is discussed in greater detail in (303) and (170). It is anticipated that genotypic methods will be adapted for use in genetic counseling in the coming years. Such methods are not yet widely applicable aside from use in certain unusual families with single gene conditions. Most experts feel that genotypic screening for persons with multifactorial disorders would still be premature; however some products are already on the market, and it seems likely that the predictive power of such methods will approach clinical utility within the next decade.

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Novel Targets for Drug Treatment in Psychiatry

Mitsumasa Kurita, Ph.D., Aintzane García-Bea, B.Pharm., and Javier González-Maeso, Ph.D.

Abstract Epidemiological studies of mental disorders show that roughly half of the population in the USA meets criteria for one or more of such disorders in their lifetimes, and nearly a quarter in a given year has a psychiatric disorder. Most of the first psychiatric medications, including antidepressant and antipsychotic drugs, were serendipitously discovered, and their molecular and cellular mechanisms of action are just starting to be explored. At present, only a handful of neurotransmitter systems are actually targeted by therapeutic drugs, which represents a major bottleneck that hampers the development of new central nervous system-active drugs. In this chapter, we review some of the recent advances in understanding the neurobiology of psychiatric disorders, current work on the basic and clinical aspects of drugs used for their treatment, and major concepts related to new targets in molecular psychiatry research.

Keywords Molecular psychiatry · Antipsychotic · Antidepressant · Schizophrenia · Depression · Drug abuse

30.1. Introduction

Psychiatric disorders such as schizophrenia, major depression, and drug abuse affect the life of millions of individuals worldwide (1–4). A cautious estimate by the US National Institute of Mental Health (NIMH) places the total costs associated with mental illnesses at well over $300 billion per year, ranking as the third most costly medical condition behind only ischemic heart disease and motor vehicle accidents (5, 6). The available symptomatic treatments are only partially successful, and therefore, the development of rational therapeutics, based on an understanding of the etiology, pathogenesis, and molecular mechanisms underlying psychiatric disorders, is imperative. Here we summarize our current knowledge of the mechanisms of action of approved drugs, as well as potential drug targets in the treatment of psychiatric disorders including schizophrenia, mood disorders, anxiety, and drug abuse.

M. Kurita, Ph.D.
Senior Research Scientist, Dainippon Sumitomo Pharma Co., Ltd., Osaka, Japan
e-mail: mitsumasa-kurita@ds-pharma.co.jp

A. García-Bea, B.Pharm.
Graduate Student, Department of Pharmacology, Faculty of Medicine and Odontology, University of the Basque Country, Bizkaia, Spain
e-mail: aintzane.garcia@ehu.es

J. González-Maeso, Ph.D. (✉)
Assistant Professor, Departments of Psychiatry and Neurology, Friedman Brain Institute, Leon and Norma Hess Center for Science and Medicine, Icahn School of Medicine at Mount Sinai, New York, NY USA
e-mail: Javier.Maeso@mssm.edu

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30.2. Substance-Related Disorders

Substance-related disorders are disorders of intoxication, dependence, abuse, and substance withdrawal caused by various substances, both legal and illegal. They are classified into two broad categories: substance use disorders (SUD), such as substance dependence and substance abuse, and substance-induced disorders (SID), such as intoxication, withdrawal, substance-related anxiety disorders, substance-induced psychotic disorders, and substance-induced mood disorders. However, general concerns in the recently published fifth edition of the diagnostic and statistical manual of mental disorders (DSM-5) (4) include whether to retain the division into these two main categories (dependence and abuse) (7, 8).

Some of the natural and synthetic compounds related to dependence and abuse include alcohol, amphetamine, caffeine, cocaine, hallucinogenic drugs (such as D-lysergic acid diethylamide (LSD), mescaline, and psilocybin), nicotine, opioids, and dissociative drugs (such as phencyclidine (PCP) and ketamine). The primary goal of SUD treatment is the attainment and maintenance of abstinence from all the substances, with the exception of replacement or substitution therapies. Although different classes of drugs of abuse have distinct molecular targets and mechanisms of action, they all have been suggested to increase dopamine transmission in the *Nucleus Accumbens* (NAc) through the mesolimbic dopaminergic system, producing the effect of reward (9, 10). Current pharmacotherapies that act directly on the dopaminergic system are effective for some but not all drug abusers (11).

Pharmacological treatments for substance-related disorders can be classified into four groups: replacement therapy, blockade therapy, aversive therapy, and relapse prevention. Replacement therapy is one of the first choices for opioid-related disorders and nicotine-related disorders. For the first group, methadone (μ-opioid receptor agonist), buprenorphine (a partial agonist at the μ-opioid receptor and an antagonist at the κ-opioid receptor), and combined buprenorphine and naloxone (an antagonist at the μ-opioid receptor) are used. In nicotine addiction, nicotine replacement therapies include nicotine gum, transdermal patch, inhalers, and nasal spray. Blockade therapy involves the use of receptor antagonists to diminish the reinforcing effects of the drug. Naloxone is used for acute intoxication by opioids, while naltrexone (opioid receptor antagonist) is used for opioid and alcohol-related disorders because of its anti-craving effect. Similarly, flumazenil ($GABA_A$ receptor antagonist) is administered for benzodiazepine overdose (12). An example of aversive therapy is the use of disulfiram to treat alcoholism. Disulfiram acts by inhibiting alcohol dehydrogenase, an enzyme responsible for metabolizing alcohol's first metabolite, acetaldehyde. The accumulation of acetaldehyde at high levels is toxic in humans, producing unpleasant symptoms when given in combination with alcohol. Among the relapse prevention therapies, several medications are prescribed, most of them in order to diminish the effects produced by substance use cessation, such as depression (13). Some examples include antidepressants (bupropion for nicotine addiction), anticonvulsants, and benzodiazepines. For nicotine addiction, varenicline (a partial agonist of the α4β2 subtype of the nicotinic acetylcholine receptor) is also commonly used, with minimal neuropsychiatric adverse effects (14–16). In 2004, the US Food and Drug Administration (FDA) approved the use of acamprosate for alcohol dependence. Although its exact mechanism of action remains unknown, it has been proposed to act through the *N*-methyl-D-aspartate (NMDA) receptor (17). Despite these pharmacological strategies, the molecular mechanisms underlying SUD remain largely unexplained (18). Furthermore, therapeutic strategies targeting substance-related disorders still remain elusive (18, 19). Current research is mostly focused on the roles of dopaminergic, endocannabinoid, glutamatergic, serotonergic, and adrenergic systems, as well as on immune-based therapies (11, 20–22).

30.3. Schizophrenia and Psychotic Disorders

Schizophrenia is a severe mental disorder that affects approximately 1% of the population worldwide (23–25). With a usual onset at ages between 15 and 35 years, this illness has been ranked by the World Health Organization as one of the top ten illnesses contributing to the global burden of disease (26). Its etiology remains unknown, although several studies suggest that schizophrenia represents the result of the combination of genetic and environmental factors (27, 28).

The symptoms of schizophrenia can be divided into three broad categories: positive symptoms (e.g., hallucinations and delusions), negative symptoms (e.g., loss or decrease in the ability to initiate plans, express emotion, or find pleasure), and cognitive symptoms (e.g., confused and disordered speech, memory problems, trouble with logical thinking, and difficulties to pay attention). Antipsychotic drugs are available since the mid-1950s, and are classified as typical, or first generation, and atypical, or second generation. Although this classification is not clearly defined, it is based on (1) the occupational coefficient between serotonin $5\text{-}HT_{2A}$ and dopamine D_2 receptors (29, 30), (2) the incidence of the so-called extrapyramidal side effects, and (3) their efficacy over the negative symptoms. Thus, typical antipsychotics (such as haloperidol, fluphenazine, perphenazine, and chlorpromazine) are principally dopamine D_2 receptor antagonists. They improve positive symptoms, but not negative or cognitive symptoms, and their main adverse effects are extrapyramidal symptoms. Atypical antipsychotics (such as olanzapine, quetiapine, risperidone, ziprasidone, paliperidone, or aripiprazole) emerged with clozapine in 1990s. These antipsychotic drugs are effective in the treatment of positive symptoms, with a lower prevalence of extrapyramidal effects. Similar to typical antipsychotics, atypical antipsychotics also have lack of effect on negative symptoms and cognitive deficits (31, 32).

Despite the high diversity for atypical antipsychotics and their chemical structures, it is believed that they all have in common a high affinity for the 5-HT_{2A} receptor and a much lower affinity for the dopamine D_2 receptor (33, 34). Clozapine is potentially helpful for those patients who do not respond to other antipsychotic medications (35). Given that antipsychotic drugs often fail to resolve the whole range of schizophrenia and other concomitant symptoms, such as anxiety and depression, complementary treatments include benzodiazepines and antidepressants (27). Unfortunately, about 30% of the patients are considered treatment resistant and will continue to experience psychotic and other symptoms despite the optimal use of available antipsychotic medications (32, 35, 36).

30.4. Mood Disorders

Mood disorders are classified in the following main groups: depressive disorder (major depressive disorder, dysthymic disorder, and non-specified depressive disorder), bipolar disorder (bipolar I disorder and bipolar II disorder, cyclothymic disorder, and bipolar disorder not otherwise specified), mood disorders due to a medical condition, substance-induced mood disorders, and mood disorders not otherwise specified. Major depressive disorder is characterized by one or more periods of depressive episodes that last for at least 2 weeks of low mood. Dysthymic disorder is a chronic condition in which depressed mood appears for more days than not for at least 2 years. Bipolar disorder is characterized by periods of low or depressed mood accompanied by manic episodes, or manic episodes only. Cyclothymia is considered a less severe type of bipolar disorder.

Currently, treatment of depression is primarily based on the monoaminergic hypothesis, suggesting an imbalance in the monoaminergic system, including serotonin, dopamine, and/or norepinephrine transmission (37, 38). Antidepressant drugs can be classified in "first generation" antidepressants, such as monoamine oxidase (MAO) inhibitors, tricyclic and other related cyclic antidepressants, and "second generation" antidepressants, such as selective serotonin reuptake inhibitors (SSRIs), selective norepinephrine reuptake inhibitors (SNRIs), selective serotonin and norepinephrine reuptake inhibitors (SSNRIs), and atypical antidepressants. Tricyclic antidepressants are serotonin and norepinephrine reuptake inhibitors, although they are not as selective as second generation antidepressants. Atypical antidepressants include those drugs of different chemical structures and molecular targets that finally modulate the monoaminergic system (e.g., bupropion, mirtazapine, nefazodone). Antipsychotics, mood stabilizers (such as lithium), and anticonvulsants (such as carbamazepine, valproate, and lamotrigine) are commonly used for the treatment of mania.

Some of the serious limitations of the treatment of depression include delay in onset of the therapeutic effect of antidepressants (3–4 weeks), and low response and remission rates. Additional receptor targets potentially involved in mood disorders and their treatments include dopamine, corticotropin-releasing factor (CRF), glucocorticoid, substance P, NMDA, and melatonin receptors, among many others (38, 39).

30.5. Anxiety Disorders

Anxiety disorders affect about 18% of the American adult population (40) and are the most prevalent class of psychiatric disorders (41). Although they often occur together, anxiety and depression are considered as two distinct psychiatric disorders. Anxiety disorders are classified into the following major types: panic attack, agoraphobia, panic disorder without agoraphobia, agoraphobia without history of panic disorder, specific phobia, social phobia, obsessive-compulsive disorder, posttraumatic stress disorder, acute stress disorder, generalized anxiety disorder, anxiety disorder due to a general medical condition, substance-induced anxiety disorder, and anxiety disorder not otherwise specified. Symptoms related to anxiety include extreme fear, shortness of breath, racing heartbeat, insomnia, nausea, trembling, and dizziness. Although neurochemical mechanisms related to the hypothalamic–pituitary–adrenal (HPA) axis, amygdala processing, and serotonin neuromodulation are involved in anxiety disorders, other neurotransmitter systems, such as GABA-ergic, glutamatergic, and noradrenergic have also been shown to play a fundamental role in anxiety-related phenotypes (42, 43).

30.6. Psychopharmacology and Neurotransmitter Receptors

Multicellular organisms function, reproduce, and grow in habitats where environmental conditions often change continuously and unpredictably. The function of these organisms requires that all the different cell types respond to environmental and cell-to-cell communication factors in a way that maintains a physiological dynamic equilibrium (or homeostasis). Extracellular mediators that communicate and coordinate cellular function include neurotransmitters, hormones, ions and lipids, as well as sensory stimuli such as photons, odorants, and taste ligands. The binding of these extracellular signal molecules to either

TABLE 30.1. G protein-coupled receptors (*GPCRs*) involved in psychiatric disorders.

Class	Ligands	Family name	Receptor name	G protein	References
Class A	Monoamines	Dopamine	D_1, D_5	Gs	(67)
			D_2, D_3, D_4	Gi/o	
		Adrenergic	α_{1A}, α_{1B}, α_{1C}	Gq/11	(130)
			α_{2A}, α_{2B}, α_{2C}	Gi/o	
			β_1, β_2, β_3	Gs	
		Serotonin	5-$HT_{1A,B,D,F}$	Gi/o	(178)
			5-ht_{1e}		
			5-$HT_{2A,B,C}$	Gq/11	
			5-HT_4	Gs	
			5-$ht_{5a,b}$		
			5-HT_6	Gs	
			5-HT_7	Gs	
		Melatonin	MT_1, MT_2	Gi/o	(764)
		Histamine	H_1, H_2	Gq/11	(283)
			H_3, H_4	Gi/o	
	Acetylcholine	Muscarinic	M_1, M_3, M_5	Gq/11	(343)
			M_2, M_4	Gi/o	
	Peptides	Opioids	μ, δ, γ	Gi/o	(765)
		Tachykinin	NK_1 (substance P)	Gs, Gq/11	(519)
			NK_2 (neurokinin A)	Gs, Gq/11	
			NK_3 (neurokinin B)	Gq/11	
		Vasopressin	V_{1A}, V_{1B}	Gq/11	(766)
			V_2	Gs	
			OT	Gq/11	
	Lipids	Cannabinoid	CB_1, CB_2	Gi/o	(767)
	Nucleotides	Purinergic	$P2Y_{1,2,4,6,11}$	Gq/11	(499)
			$P2Y_{12,13,14}$	Gi/o	
Class B	Peptides	Corticotropin-releasing factor	CRF_1, CRF_2	Gs	(547)
Class C	GABA	GABA	$GABA_B$	Gi/o	(768)
	Glutamate	Metabotropic glutamate	mGlu1,5	Gq/11	(445)
			mGlu2,3	Gi/o	
			mGlu4,6,7,8	Gi/o	

TABLE 30.2. Ligand-gated ion channels involved in psychiatric disorders.

Ligands	Family name	Receptor name	References
Monoamines	Serotonin	5-HT_3	(167)
GABA	GABA	$GABA_A$	(492)
Glycine	Glycine	GlyR	(495)
Glutamate	Ionotropic glutamate	NMDA	(769)
		AMPA	
		GluK (kainate)	
Acetylcholine	Nicotinic	mACh	(770)
Nucleotides	Purinergic	P2X	(500)

plasma-membrane receptors or intracellular receptors elicits characteristic cellular responses that, ultimately, affect the physiological responses of the multicellular organism as a whole.

Receptors have been classified according to their effector mechanisms. This functional classification includes at least five types of cell surface and intracellular receptors: voltage-gated ion channels, ligand-gated ion channels, G protein-coupled receptors (GPCRs), enzyme associated receptors, and nuclear hormone receptors (44) (see also Tables 30.1 and 30.2). GPCRs owe their name to their interaction with heterotrimeric (α, β and γ subunits) G proteins (45–47). There are ~1,000 genes encoding GPCRs in the human genome. These receptors regulate virtually all known physiological processes in mammals, and are targets of more than 40% of marketed drugs. GPCRs have in common a central core domain that is composed of seven transmembrane (TM) α-helices, with an extracellular N-terminus and an intracellular carboxyl tail (46–48). Although GPCRs have been known for more than four decades, the first crystal structure of the visual receptor rhodopsin was not solved until 2000 (49), and another 7 years were needed for the high-resolution structure of the β_2-adrenergic receptor (50–52). The recent explosion in GPCR structures (47, 53, 54), together with the crystal structure of the β_2-adrenergic receptor-G protein complex (see Fig. 30.1) (55), provides the foundation of what promises to be very exciting times for molecular pharmacology and drug discovery.

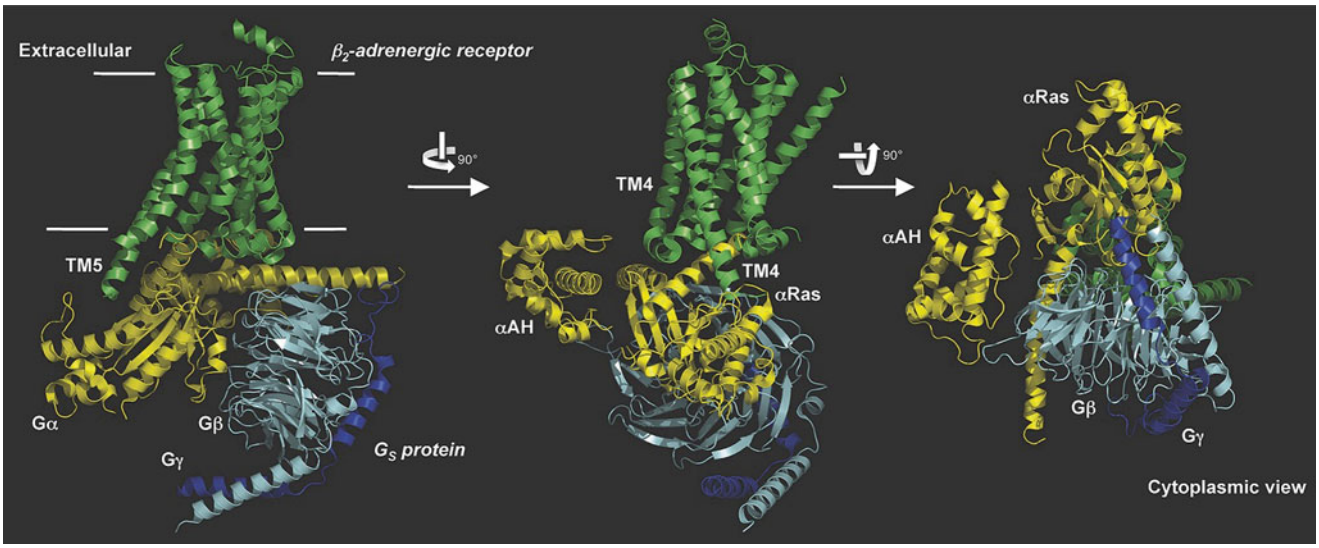

FIGURE 30.1. Structure of G protein-coupled receptors (*GPCRs*). Crystal structure of the β_2-adrenergic receptor-G_S protein complex (Protein Data Bank code 3SN6) (see Rasmussen et al. 2011). Structures of β_2-adrenergic receptor (*green*) and G_S protein heterotrimer. $G\alpha_S$ (*yellow*) together with Gβ (*cyan*) and Gγ (*purple*) constitute the heterotrimeric G protein G_S. The nucleotide-binding Gα-subunit is composed of a Ras-homology domain ($G\alpha_S$Ras) and an α-helical domain ($G\alpha_S$AH). Reprinted by permission from Macmillan Publishers LTD: Nature (55), copyright 2011.

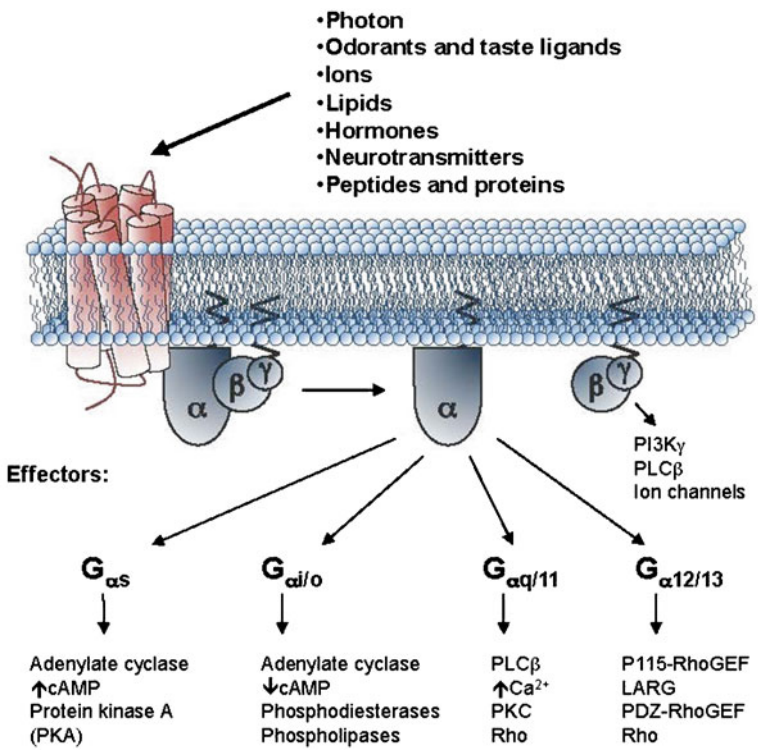

FIGURE 30.2. Receptor-G protein coupling. G protein-coupled receptors (*GPCRs*) represent one of the largest and most diverse groups of proteins encoded by the genome. Heterotrimeric G proteins are divided into four main classes based on the primary sequence of the Gα subunit: $G\alpha_S$, $G\alpha_{i/o}$, $G\alpha_{q/11}$, and $G\alpha_{12/13}$. Agonists bind to the extracellular surface of a GPCR and induce a conformational change that leads to G protein activation.

Mammals have more than 20 different G_α-subunit subtypes encoded by 17 genes. The G_α subunits form four different families ($G_{\alpha s}$, $G_{\alpha i/o}$, $G_{\alpha q/11}$, and $G_{\alpha 12/13}$) based on the degree of homology of the primary structure (see Fig. 30.2). The mechanism by which GPCRs transduce extracellular stimuli into cellular responses was initially attributed entirely to the stimulation of G protein dissociation into G_α and $G_{\beta\gamma}$ subunits, both of which can modulate the activity of downstream effectors (56–58) (see Fig. 30.2). More recently, diverse effector mechanisms for heptahelical receptors that are independent of heterotrimeric G proteins have been identified (59–62).

Parallel to these findings in structural biology, psychopharmacology is primarily organized according to a limited number of proteins that serve as binding sites for a particular neurotransmitter (e.g., GPCRs and ion channels) or that regulate a particular neurotransmitter (e.g., reuptake inhibitors or degradative enzymes) (46, 48, 63, 64).

30.7. Monoamines

Historically, there has been considerable interest in the potential role of monoamine neurotransmitters in psychiatric disorders, especially depression and schizophrenia. These include catecholamines (dopamine, norepinephrine and epinephrine), tryptamines (serotonin and melatonin), and histamine, among others.

30.7.1. Dopamine Receptors

The neurochemical and cellular effects of the neurotransmitter dopamine, which was discovered by Arvid Carlsson in the 1950s (65), are mediated by five subtypes of dopamine receptors that are divided into two major groups: D_1-like (D_1 and D_5), which are coupled to G_s proteins, and D_2-like (D_2, D_3, and D_4), which are coupled to $G_{i/o}$ proteins (66). Dopamine receptors are involved in functions such as voluntary movement, reward, hypertension, and hormonal regulation (67). In schizophrenia, the mechanism of action of antipsychotic drugs has been hypothesized to be linked to increased dopaminergic activity in the mesolimbic dopamine system (24, 68–70). Supporting this theory, all the currently prescribed antipsychotic drugs bind with high affinity to the dopamine D_2 receptor (33, 35, 71, 72). Additionally, although individual studies show contradictory findings, a meta-analysis of 13 brain imaging studies provides evidence that striatal dopamine D_2 receptor density is moderately but significantly increased in drug-naïve and in drug-free schizophrenia patients (73). In vivo positron emission tomography (PET) studies have further supported the role of dopamine D_2 receptor occupancy as predictor of antipsychotic responses (74). The authors demonstrate that antipsychotic effects correlate with a striatal dopamine D_2 receptor occupancy of 65–70%, whereas occupancy greater than 80% increases the risk of extrapyramidal side effects (75–78). Thus, the dopamine D_2 receptor has been suggested to play a significant role in the molecular mechanism of action of antipsychotic drugs.

As mentioned above, the dopamine D_2 receptor is believed to mediate its signaling response through the activation of $G_{i/o}$ heterotrimeric G proteins, which consequently negatively modulate the function of adenylate cyclase activity. To avoid detrimental effects of sustained signaling and to originate precise regulation, cells have evolved different mechanisms for reducing or suppressing the response to a stimulus. Thus, upon receptor stimulation, dopamine D_2 receptors, like other GPCRs (46, 79), acquire the suitable conformation to be phosphorylated by G protein-coupled receptor kinases (GRKs) (80–82). Phosphorylation of GPCRs by GRKs occurs at the intracellular C-terminal or at the third intracellular loop. Importantly, GRK-phosphorylated GPCRs are only minimally desensitized, but this phosphorylation increases significantly the affinity of the GPCR for β-arrestins. Binding of β-arrestins to the phosphorylated receptor blocks further G protein-dependent signaling through a steric mechanism (62, 83, 84). It has also been shown that β-arrestins bring activated receptors to clathrin-coated pits for endocytosis, a process followed by mechanisms of receptor recycling to the plasma membrane and receptor degradation (85–89). However, more recent evidence, including the crystal structure of active β-arrestin-1 bound to a fully phosphorylated 29-amino acid carboxyl-terminal peptide derived from a GPCR (90, 91), suggests that β-arrestins can also be key elements in mediating G protein-independent signaling events (61, 92). In particular, it has been shown that typical and atypical antipsychotic drugs, including haloperidol, chlorpromazine, aripiprazole, quetiapine, clozapine, olanzapine, risperidone, and ziprasidone, all antagonize the β-arrestin-2 recruitment to the dopamine D_2 receptor induced by the dopamine agonist quinpirole (93). However, these antipsychotics show various effects on D_2 receptor-$G_{i/o}$ protein coupling that range from inverse agonism and antagonism to partial agonism, which suggests dopamine D_2-β-arrestin-2-mediated signaling, and not dopamine D_2-$G_{i/o}$ protein-mediated signaling, as the molecular mechanism underlying the signaling responses that mediate their therapeutic effects (93).

Lithium as a potential drug for acute mania was serendipitously discovered by John Cade in 1949 (94), and remains the gold standard treatment for bipolar disorder today. In rodent models, acute administration of lithium salts antagonizes the locomotor hyperactivity induced by dopaminergic agonists (95–98). At the cellular level, it has been shown that lithium induces its acute effects on dopamine-dependent behaviors by blocking the action of dopamine on the Akt/GSK-3 signaling pathway in the mouse striatum. Administration of the indirect dopamine agonist amphetamine to wild-type mice elevates the dopamine tone,

which leads to cAMP-independent activation of GSK-3α and GSK-3β through a signaling pathway that requires dopamine D_2 receptors and reduced activity of Akt in the striatum. In addition, pharmacological or genetic inhibition of GSK-3 reproduces the signaling effects of lithium and reverses the behavioral responses induced by pharmacological or genetic elevation of the dopaminergic tone (99). This inactivation of Akt activity by the dopamine D_2 receptor is β-arrestin-2-dependent and requires the formation of a signaling complex that involves β-arrestin-2, Akt, and protein phosphatase 2A (PP2A). Thus, the signaling complex Akt/β-arrestin-2/PP2A regulates Akt/GSK-3 signaling and related behaviors, such as immobility time in the tail suspension test, in response to acute and chronic lithium treatment (100). It has also been demonstrated that lithium destabilizes this signaling complex without affecting other functions of β-arrestin-2, such as GPCR desensitization and endocytosis (100). These findings suggest that β-arrestin-2 is necessary to induce at least some of the dopamine-associated behavioral responses, and that its signaling complex represents a potential target for dopamine-related psychiatric disorders.

To understand psychiatric disorders, it is important to identify the neuronal circuits whose dysfunction affects behaviors that recapitulate in rodent models disease symptoms. Optogenetic tools provide a new approach to define a causal relationship between neuronal circuit activity and behavior in health and disease (101, 102). Optogenetics describes the use of microbial opsins (ion channels and pumps that can be activated by light) within intact tissue or freely-moving animals. The utility of using microbial opsins to modulate neuronal electrical activity has recently raised interest in using light to affect biochemical events and neuronal circuits that ultimately influence behavior. Dopamine neurons in the ventral tegmental area (VTA) play a crucial role in mechanisms related to stress responses and depression (103). By integrating optogenetic, pharmacological, and behavioral methods, it has been found that induction of low-frequency tonic firing, but not high-frequency phasic firing, in VTA dopamine neurons leads to a depression-like phenotype in mice as measured by social avoidance and decreased sucrose preference (104, 105). Further investigation of the neuronal circuits involved in these depression-related behaviors showed that optogenetic inhibition of the VTA-nucleus accumbens projection induces resilience to social-stress-induced behavioral abnormalities, whereas inhibition of the VTA-medial prefrontal cortex projection promotes susceptibility to social-defeat stress in freely behaving mice. These findings provide mechanistic evidence of a direct link between VTA dopamine neurons and susceptibility to depression-related behaviors, which advance our understanding of the biological underpinnings of depression and related mood disorders. A different technique termed CLARITY has more recently been described that transforms intact tissue into a nanoporous form that is fully assembled but optically transparent, allowing three-dimensional imaging and immunohistological analysis without disassembly (106). It was shown that CLARITY (an acronym to describe Clear Lipid-exchanged Acrylamide-hybridized Rigid Imaging/Immunostaining/In situ hybridization-compatible Tissue-hYdrogel) may help to shed light on structural underpinnings of neuropsychiatric disorders (106, 107).

There is considerable evidence from immunohistochemical and in situ hybridization studies that the two major subclasses of dopamine receptors, D_1 and D_2, are enriched in different populations of neurons in the neostriatum (108–111). Thus, dopamine D_1 receptors are mostly expressed in striatal neurons that contain substance P and dynorphin, projecting to the substantia nigra, pars reticulata, and entopeduncular nucleus. However, dopamine D_2 receptors are highly enriched in enkephalin-containing neurons that project to the external segment of the globus pallidus. More recent findings have shown possible co-localization of D_1 and D_2 dopamine receptors in neostriatal neurons (111). These findings suggest intracellular rather than intercellular mechanisms of the synergistic and antagonistic effects induced by activation and blockade of D_1 and D_2 dopamine receptors on numerous cellular signaling pathways (111). Preclinical studies suggest that selective D_1-like (D_1 and D_5) antagonists induce antipsychotic-like behavioral responses in rodent models. However, clinical trials with the selective D_1-like antagonists SCH39166 and NNC01-0687 showed lack of antipsychotic activity (112–114). In contrast to what has been observed with D_1-like antagonists, low doses of selective full D_1-like agonists, such as A77636 and SKF81297 have been reported to enhance cognitive function in nonhuman primates (115–117). These results suggest that activation of D_1-like receptors might represent a new approach for treatment of cognitive symptoms in schizophrenia.

The selective dopamine D_4 receptor antagonist sonepiprazole attenuates the effects of apomorphine on prepulse inhibition in rats (118). However, most of the preclinical studies indicate that sonepiprazole does not induce antipsychotic-like effects in rodents (119, 120), and this has been further supported by the lack of effectiveness of sonepiprazole for the treatment of patients with schizophrenia (121). Together, these data raise concerns as to whether D_4 receptor antagonists could have therapeutic potential in schizophrenia.

The dopamine D_3 receptor is a D_2-like receptor for which most antipsychotic drugs have high affinity. However, preliminary clinical data suggest that (+)-UH232, a dopamine D_3 receptor antagonist, does not alleviate but rather tends to worsen psychosis in drug-free schizophrenic patients (122). An association study, using a polymorphic microsatellite repeat at the D_1-like dopamine D_5 receptor, observed a difference between the allele frequencies of schizophrenia patients and controls (123).

Aripiprazole is a second generation atypical antipsychotic drug approved for clinical use in the USA and in Europe. However, and contrary to the currently marketed typical and atypical antipsychotics, aripiprazole is a partial agonist with high affinity for dopamine D_2 and D_3 receptors (124–126). It has also been shown that aripiprazole behaves as 5-HT_{1A} partial agonist and 5-HT_{2A} antagonist (127). Importantly, this antipsychotic drug does not appear to follow the same pharmacological profile that is shared by all atypical antipsychotics. Thus, aripiprazole has a greater affinity for dopamine D_2 receptor than that for the serotonin

5-HT_{2A} receptor, and it does not show transient receptor occupancy. Furthermore, PET studies in healthy volunteers demonstrate that, although aripiprazole occupies ~90% of dopamine D_2 receptors in the striatum, the extrapyramidal side effects are absent or less marked than those with typical antipsychotics. It has also been observed that aripiprazole shows dopamine D_2 receptor agonist, antagonist or inverse agonist properties depending on the heterologous system used: rat C-6 glioma cells, Chinese hamster ovary CHO-K1 cells, or human embryonic kidney HEK293 cells (124). These findings suggest that aripiprazole induces different functional outcomes depending on the particular cell type. The authors demonstrate that the antipsychotic responses induced by aripiprazole are consequence of its unique profile with distinct receptor-linked effector systems, behaving both as presynaptic D_2 receptor agonist and postsynaptic D_2 receptor antagonist (124) in the striatum. It remains to be investigated whether this pharmacological profile is involved in the antidepressant properties of aripiprazole (128).

30.7.2. Adrenergic Receptors

Adrenergic receptors have been studied intensively and extensively over the past decades, and are targets of compounds such as the so-called β-blockers that are mostly used in cardiovascular pathologies, including hypertension and myocardial diseases (129, 130). The concept of adrenergic receptor and how they were classified in α- and β-receptors based on radioligand binding and pharmacological data derived from in vivo experiments (131) served as a framework for a large body of research with other receptors such as the opioid, glucagon and muscarinic cholinergic receptors (132–134). Thus, among the many notable contributions to the development of the adrenergic receptor concept, Thomas Elliott first proposed adrenaline as a neurotransmitter (135) and Raymond Ahlquist pioneered the concept of distinct α- and β-adrenergic receptors for catecholamines (130, 136). Beginning in the 1980s, Robert Lefkowitz cloned the first GPCR gene—that of the β_2-adrenergic receptor (137), after which it became clear that seven transmembrane spans might be a shared structural feature of all GPCRs. This was confirmed by cloning the α_{2A}-adrenergic receptor the next year (138), following which a total of nine adrenergic receptors were cloned (α_{1A}, α_{1B}, α_{1C}, α_{2A}, α_{2B}, α_{2C}, β_1, β_2, β_3) (139). Over the next few years, the number of cloned receptors expanded rapidly, which confirmed the notion that the structure and signaling mechanisms are highly conserved across the large GPCR family.

The $G_{i/o}$ coupled α_2-adrenergic receptors (130) participate in functions as diverse as motor function (140), endocrine release (141), analgesia (142), sexual behavior (143), memory (144), dopamine and norepinephrine release (145), and serotonin synthesis (146). In psychiatry, these receptors have been the focus of considerable attention in fields such as depression and drug addiction. Radioligand binding assays in plasma membrane preparations and tissue sections have shown the presence of high densities of α_2-adrenergic receptors in frontal cortical regions, as well as in subcortical regions such as hippocampus, hypothalamus, and nucleus caudatus (147–149). Another region of interest in mood disorders and in which α_2-adrenergic receptors are highly expressed is the locus coeruleus (150–152). This brain region that forms part of the brainstem contains more than half of all noradrenergic neurons and sends projections throughout the central nervous system (CNS). The α_{2A}-adrenergic receptor subtype is predominantly located in frontal cortex, hypothalamus, and locus coeruleus (153, 154), whereas α_{2A}- and $\alpha_{2B/C}$-adrenergic receptor subtypes coexist in the nucleus caudatus (155). Classically, α_2-adrenergic receptors have been located in presynaptic terminals from where they inhibit the release of noradrenaline and other neurotransmitters (156–159). However, results obtained from a behavioral study suggest the importance of postsynaptic α_2-adrenergic receptors in the prefrontal cortex of nonhuman primates for cognitive behavior (160). This points out that further neuroanatomical and ultrastructural localization studies are needed with antibodies that have previously been validated in knockout mice to define whether α_2-adrenergic receptors are expressed presynaptically, postsynaptically, or both. Similarly, additional studies with knockout and tissue-specific knockout mouse models are needed to define the α_2-adrenergic subtype (α_{2A}, α_{2B}, and α_{2C}) as well as the neuronal circuits involved in these cellular and behavioral effects.

Despite these limitations in our knowledge about α_2-adrenergic receptor subtypes and their subcellular localization, preclinical and clinical studies suggest their involvement in depression and other mood disorders. Numerous studies have focused their attention on uncovering the level of expression of α_2-adrenergic receptors in postmortem human brain of suicide victims with mood disorders. Using radioligands such as the α_2-adrenergic receptor agonists [^{3}H]clonidine and [^{3}H]UK14304 in plasma membrane preparations and tissue sections, it has been suggested that the α_2-adrenergic receptor is upregulated in prefrontal cortical regions of suicide victims with major depression (147, 148). Simultaneous analyses in the same group of suicide victims with depression with the α_2-adrenergic receptor agonists [^{3}H]clonidine and [^{3}H]UK14304 and with the α_2-adrenergic receptor antagonist [^{3}H]RX821002 in the presence of the $\alpha_{2B/2C}$-adrenergic receptor antagonist ARC239 demonstrated a selective increase of α_{2A}-adrenergic receptors in frontal cortex of depressed suicide victims (149). It was also shown that agonist binding (i.e., [^{3}H]clonidine and [^{3}H]UK14304) but not antagonist binding (i.e., [^{3}H]RX821002) is enhanced in depressed suicide victims (149). Since it has been demonstrated that agonists bind with higher affinity to the active (G protein-coupled) structural conformations of the GPCRs (161, 162), together, these radioligand binding assays suggest upregulation in the active conformational state of the α_{2A}-adrenergic receptor as potentially associated with major depression. This hypothesis is supported by recent findings showing that α_{2A}-adrenergic receptor-dependent activation of heterotrimeric G proteins, measured by [^{35}S]GTPγS binding

assays (163), is upregulated in postmortem prefrontal cortex of suicide victims with mood disorders (164). Interestingly, a selective increase in the potency of UK14304 inducing [^{35}S]GTPγS binding has been confirmed in a different group of suicide victims with mood disorders and controls (165). However, although these results suggest that the α_{2A}-adrenergic receptor-G protein coupling is increased in postmortem frontal cortex of depressed subjects, it has also been shown that the α_{2A}-adrenergic receptor-dependent effects of UK14304 inhibiting adenylyl cyclase activity are reduced (165). Together, these data support the role of the α_{2A}-adrenergic receptor in prefrontal cortex as potentially involved in major depression. They also open a new line of research to investigate the molecular mechanisms and neuronal signaling pathways specifically affected by these alterations in α_{2A}-adrenergic receptor function. In this sense, some of the most recently developed tetracyclic antidepressant drugs, such as mirtazapine and mianserin, show effective antidepressant-like activity in rodents by blocking α_{2A}-adrenergic receptors (166).

30.7.3. Serotonin Receptors

Serotonin (5-hydroxytryptamine, 5-HT) is one of the oldest neurotransmitters in evolutionary terms, and has been implicated in numerous neuropsychiatric disorders, such as schizophrenia, depression, anxiety, obsessive-compulsive disorders, and drug abuse, as well as migraine, eating disorders, and vomiting (167–169). Serotonin was found as a substance responsible for the vasoconstrictor activity of serum (170–173). In 1976, Solomon Snyder postulated the presence of 5-HT binding sites in rat cortical membrane preparations (174). In 1979, the same laboratory demonstrated the presence of two distinct 5-HT binding sites, using the radioligands [^{3}H]5-HT, [^{3}H]spiperone and [^{3}H]LSD. Thus, serotonin was the only neurotransmitter that was able to displace these radioligands and consequently these two sites were named 5-HT_1 and 5-HT_2 (175). Mammalian serotonin receptors are now classified into 14 structurally and pharmacologically distinct 5-HT receptor subtypes (176–178). At the structural level, only the 5-HT_3 receptor is a ligand-gated ion channel, whereas 5-HT_{1A}, 5-HT_{1B}, 5-HT_{1D}, 5-ht_{1e}, 5-HT_{1F}, 5-HT_{2A}, 5-HT_{2B}, 5-HT_{2C}, 5-HT_4, 5-ht_{5a}, 5-ht_{5b}, 5-HT_6, and 5-HT_7 are seven transmembrane GPCRs (note that the use of lower case designates a receptor that has not been definitively demonstrated to be functional in native systems). Given that each receptor has a distinct neuroanatomical distribution in the CNS, it seems highly likely that 5-HT receptor-mediated changes in intracellular signaling pathways and gene expression play fundamental roles in neuronal plasticity and psychotropic drug therapy.

The serotonergic system modulates the responses to acute stress exposure, and has been involved in the neurobiology of depression and anxiety as well as in the therapeutic response to treatment (179–183). The $G_{i/o}$ coupled 5-HT_{1A} receptor is expressed in two distinct populations of neurons in the CNS: in serotonergic neurons of the raphe nuclei as autoreceptor where it controls serotonin tone through feedback inhibition, and in non-serotonergic neurons of the forebrain, mainly in the hippocampus, septum, and cortex, as heteroreceptor (184). Agonists of the 5-HT_{1A} receptor have been shown to have anxiolytic properties in both preclinical and clinical studies (185, 186). The contribution of 5-HT_{1A} receptors to mood control was assessed by three independent laboratories that demonstrated anxiety-like behavior in 5-HT_{1A} knockout mice (187–189). In the open field, mice without the 5-HT_{1A} receptor display decreased locomotor activity and decreased exploratory behaviors such as time in center and rearing. In the elevated plus maze, rodents face a conflict between aversion to the open arms and the motivation to explore a novel environment. Using this model, it was shown that 5-HT_{1A} knockout mice spend significantly less time in the open arms and entered into the open arms less often than control littermates (188). These results demonstrate that the 5-HT_{1A} receptor is involved in the modulation of fear-related behaviors. However, one of the limitations in the use of full knockout mice is the lack of information regarding the neurodevelopmental stage in which absence of the gene of interest affects a particular phenotype. Another question of interest regarding the role of the 5-HT_{1A} receptor in depression and anxiety was related to its presynaptic and postsynaptic sites of action. Thus, administration of the 5-HT_{1A} agonist 8-OH-DPAT locally in the raphe nuclei has anxiolytic-like effects in mice, while it is anxiogenic when administered locally in the dorsal hippocampus (190–192). To solve this puzzle, René Hen and his laboratory developed a tissue-specific conditional rescue approach with which they expressed the 5-HT_{1A} receptor in two distinct neuronal populations in mice: raphe nuclei (autoreceptor) and forebrain (heteroreceptor) (193). They also used the conditional nature of the receptor expression in this mouse model to demonstrate that 5-HT_{1A} receptor expression acts during the early postnatal period to establish normal anxiety-like behavior in the adulthood. Thus, a mouse carrying tetracycline operator (tetO) binding sites upstream of the 5-HT_{1A} receptor coding sequence was crossed with a transgenic mouse carrying the bacterial transcription factor tTA under the control of the αCaMKII promoter. This double transgenic line shows a 5-HT_{1A} receptor binding pattern similar to that observed in wild-type controls in the hippocampus and cortex, but lacks expression of the 5-HT_{1A} receptor in the raphe nuclei. Importantly, the function of the tTA protein is abolished by the drug doxycycline (193). Indeed, treatment of mice that express the 5-HT_{1A} receptor only in cortex and hippocampus with doxycycline abolishes 5-HT_{1A} expression. Using this model, it was demonstrated that restoration of 5-HT_{1A} receptors in the forebrain, but not in the dorsal raphe, reverses the anxiety-like behavior observed in 5-HT_{1A} knockout mice. They also showed that turning off 5-HT_{1A} receptor expression in adult mice does not affect anxiety-like behavior, whereas turning off 5-HT_{1A} receptor expression during postnatal developmental stages is sufficient to reverse the rescue phenotype in mice that express the 5-HT_{1A} receptor only in cortex and hippocampus (193). Together, these data suggest that expression of 5-HT_{1A} receptor in the forebrain, but not in raphe nuclei, during development is necessary for normal anxiety-like behavior in the adult.

Follow-up experiments that manipulated 5-HT_{1A} autoreceptors in the raphe nuclei without affecting 5-HT_{1A} heteroreceptors in cortex and hippocampus demonstrated the complementary point (194). They used mice containing two distinct engineered alleles. The first has tetO inserted into the promoter region of the *5-HT1A* gene (*Htr1atetO*). The second is a transgenic mouse expressing the tetracycline-dependent transcriptional suppressor (tTS) under the control of the previously characterized 540Z Pet-1 promoter fragment (*Pet1-tTS*). In the presence of doxycycline, mice homozygous for the *Htr1atetO* allele and expressing one copy of the *Pet1-tTS* show levels of 5-HT_{1A} autoreceptor similar to those observed in control littermates lacking the tTS transgene. However, removal of doxycycline gives rise to a group of mice with lower expression of 5-HT_{1A} autoreceptors. Neither presence nor absence of doxycycline affects expression of 5-HT_{1A} heteroreceptors in these mice. Using this strategy to manipulate 5-HT_{1A} autoreceptors without affecting 5-HT_{1A} heteroreceptors, the authors demonstrate that specific manipulation of 5-HT_{1A} autoreceptors in adulthood is sufficient to induce changes in reactivity to stress and response to the antidepressant fluoxetine (194).

One of the unique characteristics related to the treatment with antidepressant drugs is that, whereas most antidepressants increase levels of monoamines immediately after the first administration, their therapeutic effects require at least 3–4 weeks of treatment. Adult neurogenesis is a term that refers to the generation of new neurons in the brain of adult animals. This phenomenon is usually confined to two distinct brain areas: the subventricular zone and the subgranular zone of the dentate gyrus in the hippocampus. Recent findings elegantly demonstrate the requirement of hippocampal neurogenesis for the therapeutic-like behavioral effects induced by antidepressant drugs such as fluoxetine, imipramine, and desipramine (195). Importantly, 5-HT_{1A} knockout mice are insensitive to the effects of fluoxetine on neurogenesis in the hippocampus (195). This form of plasticity showing adult hippocampal neurogenesis as involved in some of the effects of antidepressant drugs has received considerable attention in recent years, and has provided a novel avenue for the treatment of mood disorders (196, 197).

Pharmacological and genetic studies have also suggested a role for 5-HT_{1B} receptors in the pathophysiology of psychiatric disorders such as depression, aggression, and drug addiction. Mice lacking the 5-HT_{1B} receptor do not exhibit any obvious behavioral defect (198). However, in the presence of an intruder, 5-HT_{1B} knockout mice attack the intruder faster and more aggressively than that observed in control littermates (198). Using the third intracellular loop of the 5-HT_{1B} receptor as bait in a yeast-two hybrid screen, more recent findings show that p11, a member of the S100 EF-hand protein family (199), interacts with 5-HT_{1B} receptors, but not with 5-HT_{1A}, 5-HT_{2A}, 5-ht_{5A}, 5-HT_6, dopamine D_1, or dopamine D_2 receptors (200). Investigating the functional role of p11 in heterologous systems and mouse models, it was demonstrated that overexpression of p11 increases the density of 5-HT_{1B} receptors at the plasma membrane. Furthermore, expression of p11 is increased in the forebrain of mice chronically treated with imipramine or after electroconvulsive therapy, but decreased in postmortem human brain of depressed subjects. They also generated p11 knockout mice and found that there were fewer binding sites for the 5-HT_{1B} antagonist in globus pallidus and substantia nigra pars reticulata. This reduced density of 5-HT_{1B} binding sites in p11 knockout mice correlated with a depression-like phenotype and decreased responses to antidepressant drugs. Investigation of the cell types that express p11 and its role in antidepressant responses showed that p11 is highly enriched in layer V of cortical neurons projecting to the striatum, and that loss of p11 results in decreased responses to SSRIs (201). More recent work indicates that SMARCA3, a chromatin-remodeling factor, forms a ternary complex with p11 and annexin A2 (202). The neurogenesis and behavioral responses induced by SSRIs required the p11/annexin A2 heterotetrameric complex as direct target of SMARCA3 (202). Taken together, these studies indicate that p11 dynamically modulates the function of the serotonin 5-HT_{1B} receptor in a way that affects depression-like states.

The $G_{q/11}$-coupled 5-HT_{2A} receptor has received much attention with regard to schizophrenia and psychosis, and more recently as potentially involved in mood disorders such as depression and anxiety (34, 203). The hallucinogenic properties of the semisynthetic compound LSD (D-lysergic acid diethylamide) were discovered serendipitously by Albert Hoffman in 1943 (204–206). A few years later, serotonin was found in bovine blood serum and in the brain (170–173) (see also above). In 1954, it was proposed that the psychedelic effects of LSD might be a consequence of serotonergic properties in the CNS (207). This serotonergic hypothesis about the mechanism of action of LSD was extended based on findings that identified structural similarities between serotonin and hallucinogens such as psilocybin, and the identification of serotonin as a neurotransmitter (208). Later in the 1980s, Richard Glennon, Milt Titeler, and their collaborators showed first a highly significant correlation between the affinities of 22 hallucinogenic compounds for 5-HT_2 binding sites and their hallucinogenic potency in humans (209). They also demonstrated a significant correlation between the 5-HT_2 binding affinities of these agents and drug discrimination ED_{50} values in rats (210). This milestone work, together with the identification of similarities between the alterations in cognition and perception induced by hallucinogenic drugs, such as LSD, mescaline, psilocybin, and *N*,*N*-dimethyltryptamine (DMT) in healthy volunteers, and those observed in schizophrenia patients (211–214) pointed toward a fundamental role of serotonin in general, and the 5-HT_{2A} receptor in particular, in schizophrenia and other psychotic disorders. This is further supported by recent findings with the crystal structure of the human 5-HT_{2B} receptor bound to LSD (215, 216). The generation of 5-HT_{2A} receptor knockout mice (217) and the use of the 5-HT_{2A} receptor antagonist ketanserin in healthy volunteers (218) demonstrated that this receptor is necessary for the behavioral responses induced by hallucinogenic drugs through a mechanism that involves activation of the 5-HT_{2A} receptor in cortical glutamatergic neurons (217, 219–221).

However, although these findings suggest a potential role for the 5-HT_{2A} receptor in the therapeutic responses induced by atypical antipsychotic drugs, their molecular mechanism of action has eluded the effort of researchers for more than six decades. The first antipsychotic chlorpromazine was discovered in 1952 as an antihistaminic that decreased psychosis (222). Haloperidol was originally designed as a pain reliever (223), and clozapine was described in 1958 as a "tricyclic antidepressant with neuroleptic properties" (224, 225). One of the characteristics shared by all the atypical antipsychotic drugs, such as clozapine, olanzapine, and risperidone, is their high affinity for the serotonin 5-HT_{2A} receptor together with a significantly lower affinity for the dopamine D_2 receptor, suggesting that these two receptors might be at least in part involved in the mechanism of action of atypical antipsychotic drugs, and consequently, that their range of relative affinities for serotonin 5-HT_{2A} and dopamine D_2 receptor could be used to predict their therapeutic effects. However, and importantly, it has been shown that this pharmacological profile does not correlate with the antipsychotic effects of the tested compound. For example, closely related non-antipsychotic compounds, such as ritanserin or methysergide, also block serotonin 5-HT_{2A} and dopamine D_2 receptor function, but they lack comparable antipsychotic effects (226, 227). Recent findings point toward a close molecular interaction between 5-HT_{2A} and the metabotropic glutamate 2 (mGlu2) receptor as a target potentially involved in the mechanism of action of atypical antipsychotic drugs (228–230). GPCRs have been thought to function as monomers. This monomeric model of receptor signaling is further supported by observations based on assays that measured agonist binding and G protein coupling of a single purified monomeric family A GPCR, including β_2-adrenoceptor and rhodopsin, reconstituted into nanodiscs (soluble lipid bilayer systems) (231, 232). Nevertheless, many instances of homomerization and heteromerization (macromolecular complexes formed by non-covalently bound GPCRs) have now been reported in different GPCR families (233–235). This is further suggested by the recent explosion of research elucidating crystal structures of GPCRs (47, 54), especially by the dimers found within four of the recent structures [CXCR4 (236), μ-opioid (237), κ-opioid (238), and β_1-adrenergic receptors (239)]. These X-ray crystal structures suggest that GPCRs display two dimer interfaces. One interface involves transmembrane domains 1 and 2 (TM1 and TM2) and the C-terminal H8, whereas the other interface is formed by TM4 and TM5. These and other findings suggest that GPCRs can assemble into homomeric and heteromeric structural units that affect both intracellular receptor trafficking and cellular signaling. Interestingly, it has been demonstrated that three residues located at the intracellular end of TM4 are necessary for mGlu2 to be assembled as a GPCR heteromer with the 5-HT_{2A} receptor in vitro in tissue culture and in mouse frontal cortex (see Fig. 30.3) (228, 230). Substitution of these residues (Ala-$677^{4.40}$, Ala-$681^{4.44}$ and Ala-$685^{4.48}$) leads to absence of molecular proximity between the $G_{q/11}$-coupled 5-HT_{2A} receptor and the $G_{i/o}$-coupled mGlu2 receptor, and attenuates the behavioral responses induced by atypical antipsychotic drugs (230, 240). More importantly, the 5-HT_{2A}-mGlu2 heteromeric receptor complex-mediated changes in $G_{i/o}$ and $G_{q/11}$ activity predict the antipsychotic-like behavioral effects of a variety of serotonergic and glutamatergic compounds in a *Xenopus* oocyte heterologous expression system (229). This is further supported by findings in mouse behavioral models. Thus, using MK801-induced hyperlocomotor activity as a mouse model of psychosis, it was demonstrated that the antipsychotic-like effects of clozapine are absent in mGlu2 knockout mice, and those of the mGlu2/3 agonist LY379268 are absent in 5-HT_{2A} knockout mice (229). Although further investigation is needed to validate the significance of these findings in preclinical and clinical studies, these data indicate that the signaling cross talk through 5-HT_{2A} and mGlu2 receptors as a GPCR heteromeric complex might be a causal mechanism for the induction of the therapeutic responses by atypical antipsychotic drugs (see Fig. 30.3). This pattern of G protein coupling through the 5-HT_{2A}-mGlu2 receptor complex may also be used for screening new compounds with potential antipsychotic effects. Further work is also needed to unravel the neuronal target responsible for therapeutic effects induced by atypical antipsychotic drugs. Thus, whereas the 5-HT_{2A} receptor expressed in cortical pyramidal neurons has been involved in the signaling pathways that affect behavior (229), the presynaptic component of the serotonergic system is also required for the therapeutic-like effects induced by clozapine (241).

The frontal cortex, ventral striatum, hippocampus and amygdala are brain regions highly enriched in 5-HT_{2A} receptor expression (242, 243), and these brain structures and their connecting circuits have been involved in the behavioral responses that reflect the anxiety state of the organism. Recent findings point toward a potential role of cortical 5-HT_{2A} receptor in the modulation of anxiety-like behaviors in mice. Thus, 5-HT_{2A} receptor knockout mice show reduced inhibition in conflict anxiety paradigms (such as more exploratory activity at the center portion of the open field, and greater percentage of entries made into the open arms of the elevated plus-maze), without changes observed in depression-related behaviors (such as forced swim test and tail suspension test) (244). The authors next tested whether selective restoration of 5-HT_{2A} receptor function to the cortex would rescue normal anxiety-like behavior in 5-HT_{2A} knockout mice. The 5-HT_{2A} receptor knockout mice contain a transcriptional termination sequence ("neo-stop") inserted into the 5′ untranslated region of the *5-HT2A* (*Htr2a*) gene. This neo-stop cassette is flanked by lox-P sequences, allowing it to be excised by the bacteriophage P1 recombinase (Cre). To restore 5-HT_{2A} receptor-dependent signaling to the cortex, 5-HT_{2A} receptor knockout mice were crossed with a second line of mice expressing Cre recombinase under the control of the *Emx1* promoter (244). The Emx1 is expressed in the forebrain during early brain maturation, and therefore, Emx1-Cre restores 5-HT_{2A} receptor expression only to the forebrain while leaving other sites of 5-HT_{2A} receptor expression blocked. It was observed that cortical restoration of 5-HT_{2A} receptor function normalizes the anxiety-like behavior observed in 5-HT_{2A} receptor knockout mice. Based on these findings, it is reasonable to suspect that the modulation

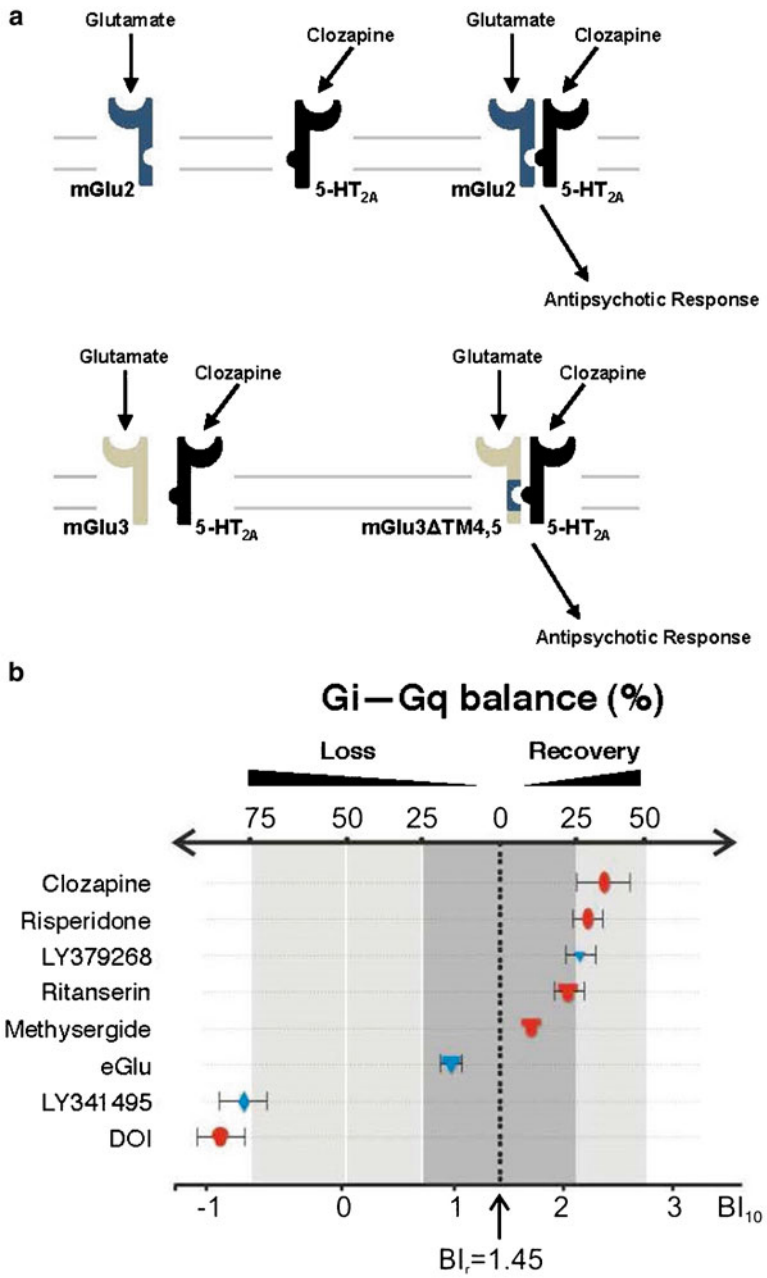

FIGURE 30.3. $G_{i/o}$–$G_{q/11}$ balance model of antipsychotic and propsychotic propensity of drugs targeting the 5-HT_{2A}-mGlu2 heteromeric receptor complex. (**a**) The $G_{i/o}$ protein-coupled mGlu2 receptor and the $G_{q/11}$ protein coupled 5-HT_{2A} receptor form a GPCR heteromeric complex in mammalian frontal cortex that integrates ligand input, modulating signaling outputs and behavioral responses. This does not occur with the closely related mGlu3 receptor. A study of a series of molecular chimaeras of the mGlu2 and mGlu3 demonstrates that three amino acid residues located at the intracellular end of the transmembrane domain 4 of mGlu2 are necessary for the formation of a GPCR complex with the 5-HT_{2A} receptor. As an example, clozapine increases glutamate-elicited $G_{i/o}$-signaling and decreases $G_{q/11}$-signaling. (**b**) The 5-HT_{2A}-mGlu2 complex-dependent changes in $G_{i/o}$ and $G_{q/11}$ activity predict the psychoactive behavioral effects of a variety of serotonergic (*red*) and glutamatergic (*blue*) compounds, including antipsychotics (clozapine, risperidone, and LY379268), neutral antagonists (ritanserin, methysergide, and eGlu), and propsychotics (LY341495 and DOI). These observations provide a mechanistic insight into antipsychotic drug action (see Fribourg et al. 2011). Balance Indexes (*BIs*) were calculated for 10 μM concentrations of the drugs (BI_{10}). Figure 30.3b reprinted in a modified form from Cell, 147(5), Fribourg M, Moreno JL, Holloway T, Provasi D, Baki L, Mahajan R, Park G, Adney SK, Hatcher C, Eltit JM, Ruta JD, Albizu L, Li Z, Umali A, Shim J, Fabiato A, MacKerell AD Jr, Brezina V, Sealfon SC, Filizola M, González-Maeso J, Logothetis DE, Decoding the signaling of a GPCR heteromeric complex reveals a unifying mechanism of action of antipsychotic drugs, 1011–1023, Copyright (2011) with permission from Elsevier.

of cortical pyramidal neuron glutamate release by 5-HT_{2A} receptor-dependent signaling is at least in part involved in the mechanisms through which cortical neurons modify the activity of subcortical structures. This hypothesis is further supported by more recent findings showing that administration of CRF into the frontal cortex enhances 5-HT_{2A} receptor-dependent anxiety-like behaviors in mice in response to the 5-HT_{2A} receptor agonist DOI (245).

The serotonin 5-HT_{2C} receptor possesses unique molecular and cellular properties such as RNA editing and constitutive activity (246). The 5-HT_{2C} receptor was identified by Ángel Pazos and collaborators at Sandoz in Basle, Switzerland, in 1984 (247). They measured the binding characteristics of [^{3}H]5-HT, [^{3}H]8-OH-DPAT, [^{3}H]LSD, [^{3}H]ketanserin and [^{3}H]mesulergide in plasma membrane preparations of pig frontal cortex, hippocampus and choroid plexus. [^{3}H]5-HT, [^{3}H]LSD and [^{3}H]mesulergide, but not [^{3}H]8-OH-DPAT and [^{3}H]ketanserin, labeled the pig choroid plexus with high affinity, and ligands that had previously been reported as selective for 5-HT_{1A}, 5-HT_{1B} or 5-HT_2 subtypes did not show affinity for these binding sites. Consequently, these 5-HT binding sites in pig choroid plexus were named "5-HT_{1C}" (247). Their subsequent finding that these 5-HT_{1C} sites are not linked to adenylate cyclase activity (248), and the identification by Elaine Sanders-Bush in 1985 that 5-HT stimulates phosphoinositide turnover linked to what they termed the "S_2 binding site" in rat cerebral cortex but not in subcortical regions (249), and once the receptors were cloned, made a shift of the "5-HT_{1C} (or S_2 binding site)" to the 5-HT_2 receptor family and its reclassification as 5-HT_{2C} unavoidable (250).

The generation of mice lacking 5-HT_{2C} receptors led to the discovery that this receptor plays a key role in the serotonergic control of appetite. Thus, 5-HT_{2C} knockout mice are overweight as a result of abnormal feeding behavior (251), and it was suggested that decreased 5-HT_{2C} receptor activity leads to increased food intake as a consequence of a behavioral alteration, rather than because of a metabolic disorder. This was further supported by findings showing compulsive-like behavior in 5-HT_{2C} knockout mice (252, 253). Obsessive-compulsive disorder (OCD) is a common and often debilitating psychiatric condition that affects 1–3% of the population worldwide (254, 255). The symptoms of OCD are characterized by persistent intrusive thoughts (obsessions), e.g., an obsession about germs and contamination; repetitive ritualistic behaviors (compulsions), e.g., attendant washing and cleaning behaviors; and excessive anxiety. Currently, the first line medications for OCDs are the SSRIs, such as fluoxetine and fluvoxamine, together with the tricyclic antidepressant clomipramine. However, only 40–50% of the patients respond to the treatment, and those who respond are often partial responders. Interestingly, it has been shown that 5-HT_{2C} knockout mice chew more of a plastic screen (252). Small plastic circular grid-style mats (conventionally used for needlepoint) were placed into the cage. After 10 days of presentation to the mice, the circular mats were examined, and mice were sacrificed to examine for plastic fragments in stomach and colon (252). They found that, although 5-HT_{2C} knockout and control littermates chewed the circular mats, the 5-HT_{2C} knockout mice did it more extensively and methodically in a characteristic well-ordered way compared to wild-types. No plastic fragments were observed in the gastrointestinal tract, which suggests that mice were not chewing the plastic mats in an ingestive manner. These findings suggest that the 5-HT_{2C} receptor contributes to OCD-like behavior, and raise the possibility that this receptor might be involved in the mechanism of action of serotonin reuptake inhibitors as drugs used to treat OCDs.

One of the unique characteristics of 5-HT_{2C} receptors is its post-transcriptional RNA editing (256). Thus, the 5-HT_{2C} receptor pre-RNA can be edited at five positions (A, B, C, D, and E), which alters the amino acid sequence in the intracellular loop 2 (a region involved in receptor-G protein coupling) (257, 258). Adenosine residues are converted to inosines through a mechanism that requires the action of double-stranded RNA adenosine deaminase(s). Editing can generate up to 32 different *5-HT2C* mRNA isoforms that translate into 24 different 5-HT_{2C} protein sequences, all of them with different signaling features. Thus, it is accepted that the human edited VSV and VGV isoforms reduce receptor constitutive activity and decrease agonist potency and receptor-G protein coupling (256). Recent findings also suggest a potential role of editing of the 5-HT_{2C} receptor in psychiatric disorders such as schizophrenia. Thus, increased expression of the unedited 5-$HT_{2C\text{-}INI}$ isoform and decreased expression of the 5-$HT_{2C\text{-}VSV}$ and 5-$HT_{2C\text{-}VNV}$ isoforms were found in frontal cortex samples (Brodmann's area [BA] 46) of schizophrenic subjects (259). More recent findings suggest *5-HT2C* mRNA editing variations in postmortem frontal cortex that are associated with suicide, but not with the comorbid psychiatric diagnoses (260), which gives support to the development of pharmacological tools to manipulate RNA editing as a potential approach to prevent suicidal behavior.

It is now clear with these findings the clinical utility of specific 5-HT receptor subtypes. Ongoing studies with 5-HT_4 (201), 5-ht_{5A} (261, 262), 5-HT_6 (263) and 5-HT_7 (264, 265) further support the common belief that 5-HT receptors can be linked with the modulation of particular behaviors and applications in clinical psychiatry.

30.7.4. Melatonin Receptors

Accumulating evidence suggests that melatonin may be involved in the pathophysiology of psychiatric disorders such as schizophrenia (266) and depression (267, 268). The hormone melatonin is secreted by the pineal gland, regulating sleep and circadian phase through the melatonin MT_1 and/or MT_2 receptors. Patients with schizophrenia commonly experience insomnia and delays in sleep onset (269). It has been reported that antipsychotic-free schizophrenic patients show decreased nocturnal secretion of melatonin (270, 271). Schizophrenia patients lack the circadian regulation of melatonin production (272), and monozygotic

twins that are discordant for schizophrenia exhibit discrepant nocturnal levels of melatonin (273). Genotyping data that analyzed two single-nucleotide polymorphisms (SNPs) at the promoter regions of the *MT1* (rs2119882 [−184 T/C]) and *MT2* (rs4753426 [−1,193 C/T]) receptor genes suggest that rs2119882 of MT_1 may be a susceptibility gene for schizophrenia associated with insomnia symptoms in schizophrenia patients (274). Thus, circadian and melatonin alterations may be associated with sleep disturbances in patients with schizophrenia, especially in the presence of positive symptoms. A double-blind, placebo-controlled study demonstrated that melatonin significantly improves the quality and depth of nighttime sleep (275), suggesting that melatonin treatment in combination with antipsychotic drugs could decrease antipsychotic-side effects and sleep disorders.

The interest in melatonin in mood disorders started back in 1979, when lower nocturnal melatonin levels in depressed patients were reported (276, 277). Agomelatine is a selective melatonin MT_1 and MT_2 receptor agonist that also behaves as a serotonin 5-HT_{2C} receptor antagonist (278). In animal models of depression, such as forced swimming test, transgenic mouse models, and chronic mild stress, agomelatine shows antidepressant-like effects that have been found superior than those induced by melatonin (279–281). Agomelatine was approved by the European Medicines Agency (EU-EMEA) for the treatment of major depressive disorders. However, although Phase III clinical trials have been conducted in the USA, agomelatine has not yet been approved by the FDA due to its toxicity issues, including hepatic failure (267, 282). Despite these limitations, the current data are consistent with the hypothesis that melatonin receptors may represent novel antidepressant targets with fewer side effects than other antidepressants, including sexual dysfunction, sleep disturbances, and discontinuation.

30.7.5. Histamine Receptors

Histamine is synthesized in several cell types of peripheral and CNS tissues (283, 284). The function of histamine is attributed to four distinct GPCR subtypes: H_1, H_2, H_3, and H_4. The $G_{q/11}$-coupled histamine H_1 receptor has been involved in mechanisms related to smooth muscle contraction and increased vascular permeability, whereas the G_s-coupled histamine H_2 receptor plays a role in stimulation of gastric acid secretion and smooth muscle relaxation. It is also currently accepted that all four subtypes of histamine receptors are expressed widely in the CNS. While recent findings suggest a contribution of histamine H_1 and H_2 receptors in brain physiology (285), the $G_{i/o}$ protein-coupled histamine H_3 receptor is of particular interest as it has been shown to modulate behavioral responses in several models of psychosis. Histamine H_3 receptors are mainly expressed in cerebral cortex, hippocampus, amygdala, nucleus accumbens, globus pallidus, striatum, thalamus, and hypothalamus (286, 287), where they function as autoreceptors in the negative feedback control of histamine release from histaminergic neurons (288). Histamine H_3 receptor antagonists reduce locomotor hyperactivity induced by methamphetamine and MK801 (289). Histamine H_3 receptor antagonists also enhance prepulse inhibition (PPI) of startle deficits in DBA/2 mice (290), which naturally have deficits in sensorimotor gating (291). Similarly histamine H_3 receptor antagonists such as thioperamide, ciproxifan, and ABT-239 improve executive function in several rodent models of cognition, working memory, and spatial memory (292–300).

Histamine H_4 receptors (coupled to $G_{i/o}$ proteins) were identified some 10 years ago by several groups simultaneously (284), and recent findings suggest their role in immune and inflammatory responses (301). However, additional studies point toward functional expression of histamine H_4 receptors in human and rodent cortex, hippocampus, thalamus and amygdala (302), which suggests their implications in CNS function. The histamine H_4 receptor antagonist JNJ-7777120 reduces rat exploratory behavior in a dose-dependent manner, which suggests a potential role of the histamine H_4 receptor in motor function and/or anxiety-like behavior (303). Although it is interesting, this hypothesis requires further investigation in preclinical models.

The sedating effect of clozapine has frequently been attributed to antagonism of the histamine H_1 receptor (304). However, recent findings suggest that selective antagonism of histamine H_1 receptors may not be the mechanism responsible for the sedating effects of atypical antipsychotics, and show that it is the cortical population of serotonin 5-HT_{2A} receptors that mediate locomotor-suppressing effects of clozapine in mice (305, 306).

30.7.6. Reuptake Inhibitors and Monoamine Oxidase Inhibitors

Treatment of depression and other mood disorders is based on drugs that were developed in the 1950s. In this decade, the compound iproniazid, originally designed for the treatment of patients with tuberculosis (307, 308), was observed to induce mood-elevating effects and to behave as MAO inhibitor. The MAOs are a family of enzymes, comprising MAO-A and MAO-B subtypes, that are localized in mitochondrial membranes and catalyze the degradation of catecholamines, serotonin, and other endogenous amines, both in the CNS and peripheral tissues (309–311). MAO-A deaminates norepinephrine and serotonin and is selectively inhibited by clorgyline. MAO-B preferentially metabolizes phenethylamine, and is inhibited by selegiline. Historically, iproniazid was the first antidepressant to be approved for the treatment of mood disorders (38, 128, 312). Two other MAO inhibitors, tranylcypromine and moclobemide, were subsequently introduced into the market.

The first tricyclic antidepressant, imipramine, was synthesized in the late 1940s as a potential antipsychotic, and found to be ineffective in psychotic patients but it showed therapeutic effects in depressed patients. Based on their pharmacological proper-

ties, antidepressant drugs are now classified into six major groups (see also above): tricyclic antidepressants, SSRIs, SSNRIs, SNRIs, MAO inhibitors, and atypical antidepressants. Tricyclic antidepressants form a rather homogeneous group all derived from imipramine. They are classified into three subgroups based on their central ring of five links: ring without heteroatoms (e.g., amitriptyline, nortriptyline, and protriptyline), heterocyclic ring with one heteroatom that is preferably nitrogen (e.g., imipramine, desipramine, clomipramine, trimipramine), and heterocyclic ring with more than one heteroatom (e.g., amoxapine, and tianeptine). This group of antidepressants is characterized by their inhibition of serotonin and norepinephrine reuptake, as well as their properties to block the function of several monoaminergic receptors. SSRIs, such as fluoxetine, paroxetine, sertraline, and citalopram, are considered chemically heterogeneous, but with similar therapeutic effects to those induced by tricyclic antidepressants. Other SSRIs, such as trazodone, show unique pharmacological effects that justify their classification into a different group of antidepressants. Inhibitors of serotonin and norepinephrine, such as venlafaxine, duloxetine, and milnacipran, share a similar function with tricyclic antidepressants (see above) in terms related to serotonin and norepinephrine reuptake. However, they bind to different types of neurotransmitter receptors, and thereby their secondary effects are different as compared to those induced by tricyclic antidepressants. Selective norepinephrine inhibitors, such as reboxetine, show low affinity for monoaminergic receptors, with minimal secondary effects.

Atypical antidepressants include a diverse array of drugs: mianserin behaves as antagonist of α_1 and α_2 adrenergic receptors, mirtazapine, structurally related to mianserin, blocks the function of α_2 adrenergic and serotonin 5-HT_{2A} receptors, and bupropion inhibits the reuptake of dopamine and norepinephrine, but not serotonin. Although understanding of the pathological mechanisms underlying mood disorders has evolved substantially, enormous gaps in the knowledge of their treatment persist. Relatively little attention has been directed toward understanding the remarkable heterogeneity in the responses to stressful life events in humans. Recently developed animal models may be used to provide insights into these clinical observations. Similarly, to improve outcomes for patients with depression, it is imperative to go beyond monoaminergic antidepressant treatment and expand our knowledge, using animal models and clinical observations, about the molecular mechanisms underlying depression and its treatment.

30.8. Acetylcholine

The concept of chemical neurotransmission is generally attributed to the seminal work of Otto Loewi and Henry Dale during the first three decades of the 20th century with which they identified acetylcholine as a neurotransmitter at parasympathetic nerve terminals (313). The effects of acetylcholine are primarily mediated through either ionotropic nicotinic receptors or metabotropic (GPCR) muscarinic receptors. Nicotine is heavily abused by schizophrenia patients (314). Approximately 90% of schizophrenic patients smoke compared to about 33% in the general population and 45–70% in patients with other psychiatric disorders (315–318). An explanation for this elevated rate of smoking in schizophrenia patients has been proposed to be a form of self-medication to treat symptoms such as anxiety, anhedonia, or amotivation (319–322). It has also been suggested that nicotine alleviates side effects induced by antipsychotic drugs (323–326). Smoking may also be related to improvements in sensory gating (326, 327), a deficit that has been observed in schizophrenia patients (328). High densities of nicotinic receptors have been discovered in the medial temporal lobe, a brain area in which expression of α7-nicotinic receptors is decreased in schizophrenic subjects (329). Additional evidence for the potential role of the α7-nicotinic receptor in schizophrenia has been provided through genome-wide linkage analysis (330), and this finding has been further replicated in additional studies (331–334). Deficits in prepulse inhibition of startle reflex as a model for the sensorimotor gating has been shown to be influenced by polymorphisms in the α7-nicotinic receptor gene (*CHRNA3*) (335). Findings in animal models also support the role of α7-nicotinic receptors in auditory gating (336). Importantly, a recent clinical trial suggests that the α7-nicotinic receptor partial agonist TC-5619 benefits cognitive dysfunction and negative symptoms in schizophrenia patients treated with quetiapine or risperidone (337). It has also been shown that the nicotinic receptor partial agonist varenicline may have some function as an antipsychotic medication (14).

Muscarinic receptors belong to the superfamily of GPCRs. There are five genes that encode muscarinic receptor proteins (M_1, M_2, M_3, M_4, and M_5) (338–341). The M_1, M_3, and M_5 receptors are coupled to $G_{q/11}$ proteins, which subsequently activate phospholipase C and calcium mobilization. The muscarinic M_2 and M_4 receptors activate $G_{i/o}$ proteins and inhibit adenylate cyclase activity and cAMP formation (342, 343). Muscarinic receptors are widely distributed in the periphery in the autonomic nervous system, including the eye, salivary and sweat glands, lungs, genitourinary tract, and cardiovascular system. Centrally, muscarinic receptors are involved in numerous processes that include memory, sensory perception, acute pain, and mood. A dysfunction of the cholinergic system has been suggested as involved in the etiology of schizophrenia (344–347). Recent phenotypic analysis of null mutant mice for each of the muscarinic receptor subtypes has raised new information regarding the physiological role of individual receptor subtypes as well as the muscarinic receptor-regulated signaling pathways as therapeutic targets for the treatment of disorders such as Alzheimer's disease, schizophrenia, and drug addiction (348, 349). One of the limitations of these findings and a major challenge for future investigation is the development of muscarinic ligands with increased therapeutic efficacy and reduced side effects.

30.9. Glutamate

Glutamate is the main excitatory neurotransmitter in the mammalian CNS and exerts its effects through the activation of ionotropic (NMDA, AMPA, and Kainate) or metabotropic receptors. Numerous lines of research suggest a significant role of the glutamatergic system in psychiatric disorders (350–357). Among these, decreased glutamate levels have been observed in cerebrospinal fluid (CSF) of schizophrenic patients (358), whereas increased glutamate levels have been reported in cortical regions and limbic brain areas of depressed patients, as well as in postmortem frontal cortex of subjects with major depression (23, 359–361). Moreover, increased glutamate activity has also been shown in the anterior cingulate cortex of alcoholic patients (362).

30.9.1. NMDA Receptors

Almost 30 years ago, patch-clamp and binding studies on neuronal preparations raised the notion that NMDA receptors are expressed as multiple subtypes (363–365). Further investigation and cloning revealed seven different subunits, subclassified into three different families: the GluN1 subunit, four distinct GluN2 subunits (GluN2A, GluN2B, GluN2C, and GluN2D) which are encoded by four different genes, and two GluN3 subunits (GluN3A, and GluN3B), which are encoded by two different genes. All GluN subunits share a common structure of the N-terminal domain, the agonist-binding domain that binds either glycine or D-serine in GluN1 and GluN3 and glutamate in GluN2, and the transmembrane domain that contains the ion channel, and the carboxyl-terminal domain. Each subunit contains from 900 to 1,480 amino acids, and the differences in subunit sizes are mostly based upon the length of the intracellular carboxyl-terminal domain (366–370).

Glutamatergic hypofunction is one of the main hypotheses underlying the pathophysiology of schizophrenia (355, 371–374). Noncompetitive NMDA receptor antagonists such as ketamine and PCP are used as pharmacological models of schizophrenia in animals because of their capacity in humans to evoke positive and negative symptoms as well as sensorimotor gating resembling those seen in this disease (375–378). The potent and selective noncompetitive NMDA receptor antagonist MK801 (dizocilpine) can also elicit ketamine-like symptoms in healthy volunteers (379). Hence, the use of NMDA-enhancing agents, such as glycine, D-serine and sarcosine, has shown beneficial effects on the negative symptoms of schizophrenia patients who have been receiving adequate treatment with atypical antipsychotics (355). Although further investigation is needed both at clinical and preclinical levels, these findings suggest that compounds that enhance NMDA function may serve as a promising new tool to improve schizophrenia treatment (355). Particularly, a relatively recent meta-analysis suggests that NMDA-enhancing molecules are effective in most schizophrenic symptom domains (380).

In depression, it has been shown that a single, low sub-anesthetic dose of ketamine may relieve depressive symptoms within hours (381). Thus, different randomized, placebo-controlled trials demonstrate the robust and rapid antidepressant effects produced by ketamine in patients with treatment-resistant major depression (381–386), making NMDA antagonism a new promising therapeutic target treatment of refractory depression (350, 356, 387–391). Similar findings have been observed in animal models of depression (392–396). A single dose of ketamine also has anxiolytic effects in rodents (397), and is able to reduce anxiety in healthy human volunteers at low doses (398). However, its propensity to produce tolerance (399) and psychotomimetic effects are the main barriers to the use of ketamine as antidepressant treatment. In this context, the stereoisomer S-ketamine is currently being studied, since its psychotomimetic side effects are thought to be minimized (400–402). These findings suggest ketamine as a possible new approach for treating mood disorders compared to the weeks or months required for standard antidepressant medications. Although further investigation is necessary, it has been shown that signaling pathways associated with mTOR-dependent synapse formation (403) and rapid synthesis of BDNF neurotrophic factor (404) contribute to the antidepressant actions of ketamine.

Memantine, another noncompetitive NMDA antagonist, has been studied as it does not produce psychotomimetic side effects (389, 405). Although its antidepressant effects have not been fully proven (406), memantine reduces alcohol cravings in preclinical studies (407–409), and improves alcohol withdrawal symptoms and dysphoric mood in alcohol-dependent inpatients (410).

In order to avoid the psychotomimetic effects of ketamine, researchers started to investigate whether subtype-selective NMDA receptor blockers could maintain an efficacious antidepressant profile while avoiding those unwanted adverse effects. Interestingly, recent studies have observed the antidepressant effects of GluN2B subunit-selective NMDA receptor antagonists in preclinical models of depression (403, 411, 412) and in humans (413, 414). Although 60% of the patients responded to CP-101,606 (traxoprodil, GluN2B antagonist) as compared to 20% of the patients that responded to placebo, the initial dose was reduced to avoid the risk of dissociative symptoms. It has also been shown that ablation of GluN2A induces antidepressant-like and anxiolytic-like effects in rodents (415). Importantly, only truncation of the intracellular domain of the GluN2A subunit of the NMDA receptor induces anxiolytic-like effects, whereas depressive-like effects are not affected. This points toward signaling mechanisms related to the C-terminus of the GluN2A subunit as potential new strategies to treat anxiety (416).

Other novel therapeutic NMDA receptor-related drugs currently tested as antidepressant are AZD6765 (383), a low-trapping NMDA channel blocker with low rates of associated psychotomimetic effects, and GLYX-13 (417), a NMDA receptor glycine-site functional partial agonist.

30.9.2. AMPA Receptors

The α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (also known as AMPA receptor) is composed of a homomeric or heteromeric complex of four subunits (GluR1-4) (418, 419). Recent findings suggest an emerging role of AMPA receptors in the treatment and etiology of mood disorders (388, 420–424). Several AMPA receptor potentiators (or ampakines), such as LY392098 and LY451646, have demonstrated antidepressant-like effects in animal models of depression (421, 425–430). Moreover, AMPA receptor potentiators produce neuronal effects in BDNF function similar to those induced by currently available antidepressants (422). Antidepressant treatment induces marked changes in AMPA receptor subunit expression that are consistent with the onset of the therapeutic effect of these drugs (431). Interestingly, enhanced AMPA receptor function accounts for the rapid antidepressant-like effects of ketamine. Several studies suggest that enhanced AMPA receptor throughput may likely account for the rapid antidepressant-like effect of ketamine (391, 411, 432). In marked contrast, however, a recent study showed increased levels of AMPA receptors in postmortem anterior cingulate cortex (BA-24) samples of subjects with major depression, but not in subjects with bipolar disorder (433). These alterations were not observed in the dorsolateral prefrontal cortex (BA-46) (433). AMPA receptor-positive modulators (ampakines) have shown inconsistent results in clinical studies for their use as cognition enhancers, with improvements as well as absence of changes in cognition (434–437). In anxiety disorders, AMPA receptor antagonists have been shown to induce anxiolytic-like effects (438), and attenuation of startle responses in animal models of posttraumatic stress disorder (PTSD) (439, 440) (see also (353)).

30.9.3. Kainate Receptors

Among ionotropic glutamate receptors, less attention has been paid to kainic acid (KA) receptors, and their implications in physiological processes remain obscure (441, 442). To date, five distinct KA subunits have been identified: GluK1, GluK2, GluK3 (formerly iGluR5-7), and GluK4 and GluK5 (formerly KA1 and KA2). Functional KA receptors contain four KA subunits, which are assembled from two dimers of two homomeric or two heterodimeric subunits. KA receptors are distributed throughout the CNS, and are involved in the regulation of activity of synaptic networks, function that occurs through mechanisms of postsynaptic depolarization and presynaptic modulation of both excitatory and inhibitory neurotransmission. KAR antagonists have been proposed to be an attractive target for development of compounds potentially useful for the treatment of neurological conditions, including pain, epilepsy and migraine. The development of specific ligands is needed to further investigate the contribution of KA receptors to health and neuropsychiatric conditions (443).

30.9.4. Metabotropic Glutamate Receptors

Metabotropic glutamate (mGlu) receptors are GPCRs characterized by a large N-terminus that consists of two lobes separated by a large cleft that contains the agonist binding site (444, 445). The group I mGlu receptors (mGlu1 and mGlu5) are coupled to $G_{q/11}$ proteins and activation of phospholipase C. The group II (mGlu2 and mGlu3) and group III (mGlu4, mGlu6, mGlu7, and mGlu8) mGlu receptors are coupled to $G_{i/o}$ proteins, which typically inhibit adenylyl cyclase activity. With the exception of mGlu6 receptor, which is expressed restrictedly at the postsynaptic site of retinal ON-bipolar cells, mGlu receptors are widely distributed in the CNS. Group I and group III mGlu receptors are localized mostly postsynaptically and presynaptically, respectively, whereas group II mGlu receptors appear to be both presynaptically and postsynaptically.

Group II mGlu receptors have been extensively studied as potential new targets for the treatment of psychiatric disorders. mGlu2/3 receptor agonism blocks the cellular and behavioral effects induced by psychotomimetic agents (446–449). Activation of mGlu2/3 receptors also displays rapid anxiolytic-like activity (450) and has been of interest for the treatment of addiction to various drugs, including ethanol, cocaine, opiates, and nicotine (354). Regarding the anxiolytic-like properties of mGlu2/3 orthosteric agonists, it has been described that both mGlu2 and mGlu3 are necessary for the therapeutic effects of LY354740 (451). This compound and LY379268, another mGlu2/3 receptor agonist, are also efficacious in rodent models of ethanol, nicotine, cocaine, and morphine addiction (354, 452). On the contrary, mGlu2/3 receptor orthosteric antagonists have been suggested as a potential new approach for novel antidepressants (406, 453).

Although mGlu2/3 receptor agonists are studied as new potential antipsychotic drugs (351, 355, 454–456), different approaches in mGlu2 knockout and mGlu3 knockout mice have demonstrated that their antipsychotic-like actions are exerted through a mechanism that requires mGlu2 receptor expression, but not mGlu3 receptor expression (457–459). The first clinical trials with the mGlu2/3 receptor orthosteric agonist LY404039 (active compound of LY2140023) suggested that LY2140023 represents a potential new approach to treat schizophrenia (460). However, in two follow-up studies, Eli Lilly and Company published double-blind phase 2 clinical trials showing that neither LY2140023 nor olanzapine was more efficacious than placebo (461), which are inconclusive findings, and that LY2140023 does not separate from placebo whereas the positive control risperidone was efficacious (462). It has also been reported that improvement in the Positive and Negative Syndrome Scale (PANSS) over the initial 6–8 weeks of treatment was similar between schizophrenia patients treated with LY2140023 or stan-

dard of care (SOC: olanzapine, risperidone, or aripiprazole) (463). However, and importantly, improvement was significantly greater in the SOC group after 24 weeks of treatment (463). These findings preceded the press release that announced the decision to stop the ongoing phase 3 clinical trial of the orthosteric mGlu2/3 agonist for the treatment of schizophrenia (464). These discouraging findings contrast recent publications with the allosteric positive modulator of the mGlu2 receptor ADX71149 from Addex Inc. in partnership with Janssen R&D (465). The clinical data show safety and tolerability and demonstrate an effect in negative symptoms of schizophrenia patients (465). Although it is promising, more molecular, preclinical, and clinical data are needed to validate whether activation of the mGlu2 receptor may serve as a new approach to treat this psychiatric disease. Similarly, whether the antipsychotic-like effects of orthosteric mGlu2/3 and allosteric mGlu2 receptor agonists require expression of the 5-HT_{2A} receptor (see also Fig. 30.3, above) remains to be investigated (228–230).

Extensive research also supports the potential therapeutic effects of mGlu5 receptor positive modulation for the treatment of schizophrenia (354, 455, 466), and mGlu5 receptor blockade for the treatment of major depression (388, 406, 453, 467), anxiety (450), and addictive behavior (354). A number of positive allosteric modulators (PAMs) have been shown to be effective in preclinical models of schizophrenia (455, 468–473), and they also ameliorate cognitive dysfunction induced by NMDA receptor hypofunction (354, 474). Importantly, there is evidence of the existence of a direct functional interaction between mGlu5 and NMDA (471, 474–478), suggesting that a positive modulation of mGlu5 receptor might induce antipsychotic effects by restoring NMDA receptor function. On the other hand, mGlu5 antagonists, such as MPEP (2-methyl-6-(phenylethynyl)-pyridine) and MTEP (3-[(2-methyl-1,3-thiazol-4-yl)ethynyl]-pyridine), induce antidepressant-like effects in animal models of depression (388, 406, 453, 479–481), whereas mGlu5 knockout mice display an antidepressant-like behavioral phenotype (482). Similarly, mGlu5 antagonists have shown to exert anxiolytic-like effects in several anxiety-like behavior tests, as well as to reduce addictive behaviors in animal models (354, 483).

Recent findings provide evidence of increased expression of mGlu5 (484), as well as abnormalities in mGlu5-dependent signaling patterns in individuals with autism (485), schizophrenia and mood disorders (486), which may open a new avenue for the treatment of these psychiatric disorders.

30.10. Inhibitory Neurotransmitters: GABA and Glycine

γ-Aminobutyric acid (GABA) is the major inhibitory neurotransmitter in the CNS (487). This GABA-mediated inhibition is mediated through two classes of plasma membrane receptors. The ionotropic $GABA_A$ receptors are ligand-gated ion channels that mediate fast synaptic inhibition (487, 488). The metabotropic $GABA_B$ receptors are GPCRs that mediate the slower inhibitory actions of GABA (489–491). $GABA_A$ receptors are heteropentameric chloride channels in which each of the five subunits consists of four transmembrane domains with both N-terminus and C-terminus located extracellularly. Currently, 19 subunits have been cloned in the mammalian CNS: α(1-6), β(1-3), γ(1-3), δ, ε, π, θ, ρ(1-3) (492), with receptors formed by α, β, and γ subunits being the most common. The role of $GABA_A$ receptors in mood disorders has been of great interest because they are targets of CNS-active compounds such as benzodiazepines (e.g., diazepam, clorazepam, zolpidem, and zopiclone) and barbiturates (barbital and phenobarbital). This potential role of $GABA_A$ receptors is further supported by findings in postmortem human brain showing alterations in numerous subunits of the $GABA_A$ receptor in subjects with depression (486, 487), schizophrenia (486), and autism (484, 493). Substantial evidence also suggests that cortical GABAergic neurotransmission is altered in patients with schizophrenia. Studies in postmortem human brain have provided consistent evidence that GAD67 (an enzyme responsible for most GABA synthesis) is downregulated in frontal cortex of schizophrenic subjects (494). These findings suggest that $GABA_A$ receptors represent excellent targets for the development of novel therapeutic drugs.

Glycine receptors (GlyRs) are ligand-gated chloride channels that mediate fast inhibitory neurotransmission in the spinal cord and the brainstem (495). They play an important role in motor control (496) and pain perception (497). Recent studies presented conclusive evidence supporting the role of GlyRs in the control of cell migration and postnatal brain development (495). Although it is interesting, pathological consequences derived from malfunction of GlyRs are yet to be clarified.

30.11. ATP and Other Purines

In 1972, it was shown that adenosine 5′-triphosphate (ATP) behaves as a transmitter in non-adrenergic and non-cholinergic inhibitory nerves in guinea pig taenia coli smooth muscle (498). Currently, seven subtypes of purinergic ionotropic P2X receptors and eight subtypes of purinergic metabotropic P2Y receptors are known to exist (499, 500). The $P2X_7$ receptor was suggested to be potentially involved in major depression (501) and bipolar disorder (502). The nucleoside transport inhibitor dilazep affects the clonidine-induced aggressive behavior, and this effect was suggested to be related to central purinoceptor

stimulation (503). The potential role of ATP receptors in schizophrenia was raised based on reports that showed that antipsychotic drugs, such as haloperidol and chlorpromazine, inhibit ATP-mediated responses by P2X receptors (504). Although these findings are promising, the use of purinergic drugs as therapeutic agents has yet to reach the clinic.

30.12. The Endocannabinoid System

Alterations in the endocannabinoid system have been described in a vast variety of diseases (505). Endocannabinoids are synthesized "on demand" from membrane phospholipids in response to intracellular calcium and immediately released to activate $G_{i/o}$-protein coupled CB_1 and CB_2 receptors. In neurons, where density of CB_1 receptors is highest, stimulation of presynaptic CB_1 receptors inhibits neurotransmitter release. CB_2 receptors are mostly expressed in immune cells, where they play an important role in inhibition of pro-inflammatory cytokine production (506, 507). Upregulation of CB_1 receptors in prefrontal cortex may be associated with the pathology of schizophrenia and cannabis use (508). Elevated levels of CB_1 receptor-mediated G protein signaling have also been observed in postmortem human brain samples of depressed suicide victims (509) and in alcoholic suicide victims (510). Interestingly, in vivo exposure to Δ9-tetrahydrocannabinol (THC) abolishes the retrograde signaling that underlies endocannabinoid-mediated synaptic plasticity in both NAc and hippocampus, revealing a molecular mechanism by which cannabis derivatives may alter cognitive functions and motivational behaviors (511). Further investigation is needed to define the therapeutic implications of these findings.

30.13. Peptide Neurotransmitters and Hormones

30.13.1. Opioids

Opioid receptors are GPCRs whose signaling mechanisms involve activation of $G_{i/o}$ proteins, with downstream inhibition of adenylate cyclase activity and opening of K^+ channels. Cloning studies have identified three subtypes of opioid receptors: μ-, δ-, and κ-opioid receptors (512). Opioids are typically related to their function in processes related to analgesia, euphoria, depression of respiratory drive, and liability for addiction (513). However, recent findings suggest that the δ-opioid receptor (DOR) may represent a new target for antidepressant and anxiolytic therapy (514–517). A number of compounds have demonstrated anxiolytic and antidepressant effects in animal studies. Currently, two DOR agonists are in Phase II development for major depressive disorders: AZD-2327 and AZD-7268 (128).

30.13.2. Substance P

Tachykinin peptides are a group of neuropeptides that include substance P, neurokinin A (NKA), and neurokinin B (NKB) (518–520). These peptides are widely distributed in the CNS with distinct expression patterns, and play an important role in reproductive functions, nociception, and other physiological processes (521). The biological responses of substance P, NKA, and NKB are mediated through activation of the GPCRs named as NK_1, NK_2, and NK_3 receptors, respectively. NK_1 receptors are located at high density in the hypothalamus, periaqueductal gray matter, amygdala, locus coeruleus, and parabrachial nucleus (522). In rodent models, behavioral and physiological stress have been linked to increases in substance P, effect that is attenuated by the administration of an NK_1 receptor antagonist. It has also been suggested that after exposure to stressful situations, patients with major depressive disorder exhibit elevated CSF concentrations of substance P, and decreased serum levels have been associated with the therapeutic effects of antidepressant drugs (523, 524). Preclinical assays suggest that NK_1 receptor antagonists induce antidepressant-like effects (525, 526). This hypothesis was further supported by the antidepressant efficacy of MK-869 in a placebo-controlled clinical trial (525). However, subsequent controlled studies have not corroborated this finding (527).

30.13.3. Vasopressin

The peptide vasopressin, which is synthesized in the paraventricular nucleus of the hypothalamus as well as in the supraoptic nucleus (528), is known to play an important role in the hydromineral balance, but there is also evidence of its implication as a regulator of pituitary adrenocorticotropic hormone (ACTH) secretion (529, 530). The actions of the neuropeptide vasopressin are mediated via activation of GPCRs: vasopressin V_{1A}, V_{1B}, and V_2 receptors, which are widely distributed in the CNS in regions that include lateral septum, cortex, and hippocampus (531–533). Alterations in vasopressin levels and vasopressin receptor densities have been suggested in subjects with major depression (534–537) and obsessive-compulsive disorders (538).

It has been demonstrated that dysregulation of HPA axis function in depression may be associated with increased vasopressinergic control of the axis (539, 540). Consequently, normalization of this vasopressinergic activity through the blockade of vasopressin receptors may represent a new target for the treatment of depression and stress-related disorders (541). In rodent models, the non-peptidergic antagonist targeting vasopressin V_{1B} receptors, SSR149415, has been shown to block several endocrine, neurochemical, and autonomic responses induced by stress exposures (542, 543). In clinical studies, SSR149415 was safe and well tolerated. However, the drug was discontinued as it failed to satisfy efficacy in two major depressive disorder studies (520). Further studies are needed to develop V_{1B} receptor antagonists as well as potential biomarkers in patients who are potentially responsive to these compounds.

30.13.4. Corticotropin-Releasing Factor

In 1981, corticotropin-releasing factor (CRF) was isolated from sheep hypothalamus (544). Its characterization demonstrated that CRF is one of the principal physiological regulators of stress (545, 546). CRF binds to at least two GPCRs: CRF receptor 1 (CRF1) and CRF receptor 2 (CRF2) (547). CRF modulates behavioral responses to stress through the regulation of hormone secretion by the HPA axis (548, 549). However, it has also been shown that CRF receptors are widely expressed in different brain regions, such as neocortical areas, hippocampus, basolateral amygdala, VTA, pontine gray lateral dorsal tegmentum, and pedunculopontine tegmental nucleus (545). Importantly, basic research findings in rodent models support the notion that non-peptide CRF1 receptor antagonists induce anxiolytic-like effects. Regarding the molecular mechanism through which CRF1 receptor antagonists regulate anxiety behavior, recent findings suggest CRF1 receptor-mediated increases in 5-HT_{2A} receptor-dependent signaling (245). The authors tested the effect of CRF1 receptor expression on subcellular localization of 5-HT_{2A} receptor, and found that activation of CRF1 receptor increases rapid recycling of 5-HT_{2A} receptor, which ultimately results in increased expression of 5-HT_{2A} receptors at the plasma membrane. This cross talk between CRF1 and 5-HT_{2A} receptors was mediated through a mechanism that required intact PDZ-binding motifs at the C-terminal tails of both receptors (245). Based on these findings, it was suggested that activation of CRF1 receptors sensitizes 5-HT_{2A} receptor-dependent anxiety-like behavior, suggesting that selective blockade of CRF1 receptors may represent a new approach to treating anxiety. This hypothesis has been further supported by recent clinical trials with the CRF1 receptor antagonist NBI-30775 (also known as R121919) (550). However, although these studies yielded promising results, the compound was discontinued because of liver toxicity.

30.14. Neurotrophins: BDNF and GDNF

Brain-derived neurotrophic factor (BDNF) and glial cell line-derived neurotrophic factor (GDNF) are members of the neurotrophin family, a small family of secreted proteins that also includes nerve growth factor (NGF), neurotrophin 3 (NT-3), and neurotrophin 4 (NT-4) (520, 551, 552). Neurotrophins BDNF, NT-3, and NT-4 bind to p75NTR (also known as TNFRSF16) and to one of the three subtypes of tropomyosin-related kinase (TRK, also known as NTRK) receptors (see Fig. 30.4). Thus, NGF binds to TRKA, BDNF and NT-4 bind to TRKB, and NT-3 binds to TRKC (553, 554). Four different GDNF family ligands (GFL)—GDNF family receptor (GFRα) binding pairs have been reported in mammals: GDNF–GRFα1, neurturin (NRTN)–GFRα2, artemin (ARTN)–GFRα3, and persephin (PSPN)–GFRα3. They all signal through the receptor tyrosine kinase, RET. Recent findings suggest a critical role of BDNF in different components related to neuropsychiatric disorders such as depression and drug abuse.

The mesolimbic pathway composed of dopaminergic neurons that project from the VTA to the NAc has been involved in mechanisms related to identification of emotionally salient stimuli in the environment, in learning about the outcomes linked to those stimuli, and in ultimately defining the appropriate response (i.e., avoidance or approach) (103, 555–558). In mice, social defeat stress mimics several pathological alterations of depression, which can be normalized by chronic, but not acute, administration of antidepressants (559). Notably, it has been shown that mesolimbic dopamine pathway-specific deletion of BDNF opposes the development of depression-like behavior after social defeat stress (560), and supports the role for BDNF in mediating the behavioral plasticity in response to adverse life events. Chronic defeat stress also induces long lasting downregulation of two out of five *Bdnf* splice variant mRNAs (III and IV), and increases di-methylation of lysine 27 on histone H3 (H3K27me2, a repressive histone modification marker) at their corresponding promoters. This repressive epigenetic mark was reversed by chronic treatment with the antidepressant imipramine (561). While stressful life events are also an important cause of neuropsychiatric disorders, most individuals exposed to extreme stress maintain normal psychological functioning. This raises questions about the molecular mechanisms underlying resilience (562). Recent findings demonstrate increased BDNF immunoreactivity in NAc as a molecular signature of susceptibility to stressful life events in mice (563). Taken together, these results suggest that changes in chromatin architecture at the *Bdnf* gene and BDNF protein expression may underlie the deleterious effects of stress in rodent models.

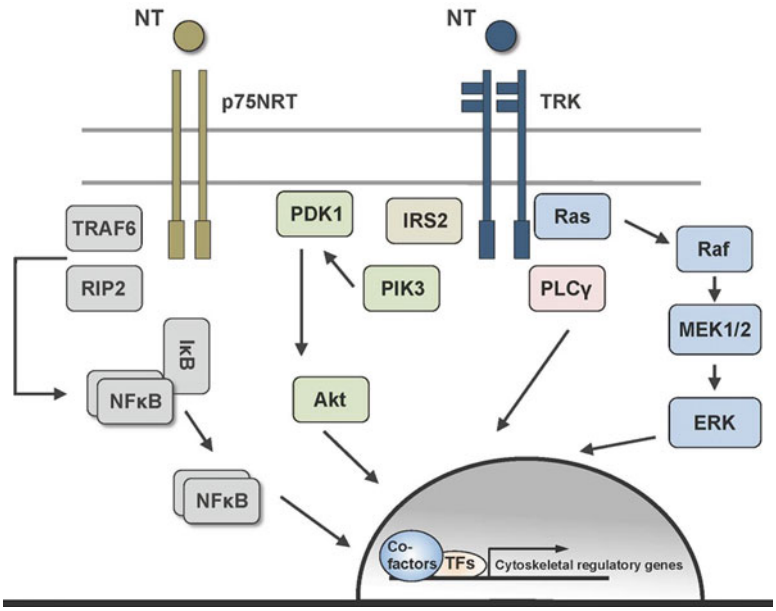

FIGURE 30.4. Cellular signaling pathways involved in the structural changes that occur in response to neurotrophins. Neurotrophins BDNF, NT-3, and NT-4 bind to p75NRT and to one of the TRK receptors, and they activate signaling pathways that ultimately control actin cytoskeletal dynamics. Recent results support the hypothesis that BDNF contributes to the therapeutic action of antidepressant effects.

BDNF has also been involved in the mechanisms underlying cocaine reward and morphine action (551, 564, 565). Striatal medium spiny neurons are divided into two subtypes based on their expression of dopamine receptors: one group expresses predominantly dopamine D_1 receptors, whereas the other expresses dopamine D_2 receptors (see above for discussion). It has been demonstrated that deletion of TRKB receptor, the BDNF receptor, selectively from dopamine D_1 receptor positive neurons enhances cocaine-induced locomotor activity after repeated cocaine administration, whereas deletion of TRKB receptor selectively from dopamine D_2 receptor positive neurons shows decreased locomotor response to cocaine (566). Thus, BDNF behaves as a key positive regulator of neuronal plasticity, promoting the psychostimulant action of cocaine. Interestingly, opposite effects for BDNF were found in response to chronic morphine exposure (567). These findings demonstrate that abolishing BDNF-dependent signaling in the VTA significantly increases the ability of morphine to promote reward, which opens a new line of research to explore the mechanisms through which the BDNF-stimulant feed-forward loop as compared to the BDNF-opiate negative feedback loop play a role in addiction.

30.15. Transcription Factors and Regulators: CREB and NFκB

Regulation of gene expression is considered as one of the mechanisms involved in psychiatric disorders and their behavioral abnormalities. Among these, transcription factors such as cAMP response element binding protein (CREB) (568) and nuclear factor kappa B (NFκB) (569, 570) have been the focus of much attention in recent years.

Several lines of research suggest that CREB in the NAc mediates the behavioral responses to drugs of abuse. Using recombinant Sindbis pseudovirions to express constitutively active or dominant-negative forms of CREB in slice cultures of the rat NAc, it was shown that active CREB increases the excitability of medium spiny neurons, whereas dominant-negative CREB induces opposite effects (571). Regarding the potential role of CREB in anxiety-like symptoms, the use of *CRE-LacZ* transgenic mice has provided clear evidence that social isolation decreases CRE-mediated transcriptional activity in the NAc, which correlates with increased expression of certain K^+ channels and reduced electrophysiological excitability of NAc neurons (572). Recent findings also suggest that BDNF-TRKB-CREB signaling in the NAc may be potentially involved as one of the signaling pathways through which drugs of abuse and stress trigger behavioral adaptations (573), and provide the route for the development of new therapies for these psychiatric disorders.

30.16. Small Rho GTPases: Rac1

Small GTPases, with molecular weights of 21–30 kDa, are monomeric guanine nucleotide binding proteins related to the α subunit of the heterotrimeric G proteins (574). They are divided into at least five families, including Ras, Rho, Rab, Arf, and Ran. Small GTPases have been traditionally involved in major aspects of cancer development, such as cell proliferation, migration, cell polarity and invasion (575, 576). However, recent findings suggest the participation of Rac1 (one of the Rho GTPase members: RhoA, Rac1, and Cdc42) in mechanisms of cocaine-induced structural plasticity as well as in mood disorders.

Dendritic spines are highly plastic and dynamic (577, 578), and have been shown to play essential roles in neuropsychiatric disorders (570). The formation of new spines depends on remodeling of the actin cytoskeleton, with Rho GTPases particularly involved in dendritic remodeling (579). Overexpression of dominant negative mutants of Rac1 or local knockout of Rac1 increase the density of immature dendritic spines on NAc neurons. It was also demonstrated that downregulation of Rac1 in NAc promotes behavioral responses to cocaine exposure, whereas activation of Rac1 induces the opposite effect (580).

After chronic social defeat stress as a mouse model of depression, recent findings revealed a reduction of Rac1 expression in the NAc (581). This expression correlated with repressive histone modifications at the promoter region of the *Rac1* gene. Importantly, similar epigenetic changes were found in the NAc of subjects with major depressive disorders in two separate cohorts. Viral-mediated reduction of Rac1 activity in the NAc was shown to increase depression-like behavior through a Rac1-dependent mechanism that affects synaptic structure (581). These findings suggest a new therapeutic venue to target plasticity mechanisms in depression and drug abuse.

More recent findings suggest a significant increase in Rac1 protein in frontal cortex of children with autism as compared to controls (485), which open the door to potential targeted treatments which could help ameliorate the symptoms of autism.

30.17. Mammalian Target of Rapamycin (mTOR)

In the 1970s, a new antifungal activity was discovered in soil samples from the Polynesian island of Rapa Nui (582–584). The active compound, which was isolated from *Streptomyces hygroscopicus*, was named rapamycin. Before its mechanism of action was understood, rapamycin was widely studied as an immunosuppressant, and, in 1999, it was approved for therapy after transplantation. Since then, rapamycin and similar derivatives have been approved for uses that range from reduction of arterial stenosis after angioplasty to cancer treatment (584). Experiments in *Saccharomyces cerevisiae* identified the genes TOR1 and TOR2 as mediators of the growth inhibitory effects of rapamycin, after which the mTOR protein was purified and showed to be the molecular target of rapamycin (582). mTOR is a serine/threonine protein kinase of the phosphatidylinositol-3-OH kinase (PI3K) family that plays fundamental roles in mechanisms of cellular growth, metabolism, proliferation and intracellular trafficking. It has been shown that mTOR functions in two distinct protein complexes: mTOR complex 1 (mTORC1) and mTOR complex 2 (mTORC2). Rapamycin inhibits mTORC1 through a mechanism that involves binding to the FK506-binding protein FKBP12, which, consequently, interacts directly and physically with mTORC1, decreasing its function (see Fig. 30.5a). mTORC2 is not directly affected by rapamycin. However, chronic exposure to rapamycin sequesters mTOR from mTORC2, inhibiting mTORC2 protein complex formation and its function (see Fig. 30.5b). Dysregulations of multiple elements of the mTOR pathway have been reported in many types of cancer. In addition, a series of studies showed that mTOR modulates processes related to neurodevelopment, cognition, memory, Parkinson's disease, schizophrenia, and drug abuse.

Disrupted-in-schizophrenia 1 (*DISC1*) is a gene involved in neurodevelopmental processes that has been linked to major mental illnesses such as schizophrenia. Previous studies have revealed that DISC1 directly interacts with the AKT binding partner KIAA1212, which prevents AKT activation in vitro (585). The functional consequences of this finding were addressed with the investigation of aspects related to embryonic and adult neurogenesis. Importantly, it was found that genetic manipulations that enhance AKT signaling in adult-born neurons induce similar effects to those induced by DISC1 suppression in neuronal development. This can be rescued by pharmacological inhibition of mTOR, an AKT downstream effector (585). The authors conclude that the AKT-mTOR signaling pathway is target of DISC1 in the modulation of neuronal development, where functionally converging signaling pathways contribute to the etiology of neurodevelopmental psychiatric disorders. This potential role of mTOR as a new target for the treatment of neurodevelopmental disorders is further supported by recent findings in schizophrenia models. The proteomic characterization by pull-down assays and mass spectrometry of the serotonin 5-HT_6 receptor-associated proteins showed that this receptor physically interacts with several proteins of the mTOR pathway, including mTOR (586). Activation of the 5-HT_6 receptor in rodent prefrontal cortex increased mTOR signaling, and rapamycin prevented cognitive deficits induced by 5-HT_6 agonists in behavior models of social cognition and novel object discrimination. Using two neurodevelopmental models of schizophrenia (neonatal PCP treatment and post-weaning isolation rearing), the activity of mTOR was increased in frontal cortex (586). Together, these findings suggest that recruitment of mTOR by 5-HT_6 in prefrontal cortex may play a role in the cognitive deficits of schizophrenia patients.

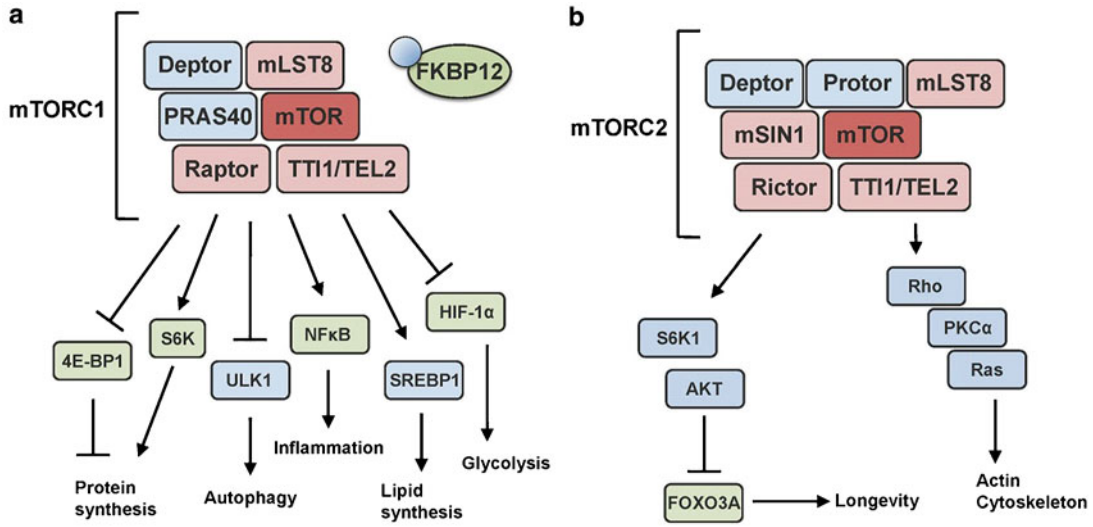

FIGURE 30.5. mTOR functions in two distinct complexes: (**a**) mTORC1 and (**b**) mTORC2. These two mTOR complexes regulate different downstream processes, including autophagy, inflammation and actin cytoskeleton assembly. Drugs that differentially affect the function of mTOR may represent a new target in the treatment of neuropsychiatric disorders.

A novel role for AKT-mTORC2 signaling in the neuroadaptations induced by the abuse of opiate drugs has been suggested in rodent models (587). Thus, chronic morphine decreased levels of phospho-AKT at Ser-473, and decreased phosphorylation of PKCα, targets of mTORC2, in mouse VTA. In contrast, levels of phospho-S6 and phospho-p70S6K, targets of mTORC1, were increased (587). Importantly, viral-mediated overexpression of Rictor, a component of mTORC2, reversed the effects of chronic morphine on cell morphology and locomotor activity, and local knockout of Rictor in VTA reduced the rewarding responses to morphine, demonstrating a potential involvement of AKT-mTORC2 signaling in the neuroadaptations to morphine and other opiate drugs of abuse.

Dyskinesia induced by L-DOPA is a rate-limiting side effect in the treatment of Parkinson's disease. It was recently found that L-DOPA-induced dyskinesia is mediated by activation of mTOR in the striatum (588). Mechanistically, the small G protein Rhes (also known as Rasd2) has recently been found to bind to and activate mTOR in mouse striatum. The therapeutic benefits for Rhes were further supported with findings in Rhes knockout mice (589). Thus, these mice showed reduced mTOR signaling and diminished dyskinesia, but maintained the motor benefits induced by L-DOPA treatment. These and other findings that suggest a mechanism through which mTORC2 controls actin polymerization, which is ultimately required for consolidation of long-term memory (590), support the hypothesis that mTOR could be a therapeutic target for the treatment of neuropsychiatric conditions. The recent co-crystal structure of mTOR and mLST8 (591) opens a new line of research for understanding mTOR function and inhibition by rapamycin and ATP-competitive compounds.

30.18. Glucocorticoid Pathway (HPA Axis)

The HPA axis is the major pathway responsible for adaptive physiological response to stress (592, 593). Briefly, upon stress exposure, CRF is released from the hypothalamus, after which it stimulates the adenohypophysis and causes the secretion of adrenocorticotropin that consequently reaches the adrenal cortex, where glucocorticoids are synthesized and released (see Fig. 30.6). The neuroendocrine stress response is dominated by glucocorticoids, which also exert a negative feedback on the release of adrenocorticotropin and CRF (592–594).

Disturbances in HPA function have extensively been associated with neuropsychiatric disorders such as schizophrenia, depression, and anxiety (595–600). Moreover, HPA dysregulation has been proposed to be a consequence of a suboptimal intrauterine environment. Environmental events during pregnancy such as maternal infection and maternal adverse life events are among the most important environmental risk factors associated with neurodevelopmental psychiatric disorders such as schizophrenia and autism (601) (see also below). Maternal stress during pregnancy leads to hyperactive HPA-axis in the adult offspring, which contributes to attention deficits, cognitive impairments, anxiety, depression, and schizophrenia (602, 603). Although these and other findings suggest the existence of similarities between prenatally stressed rodents and humans with

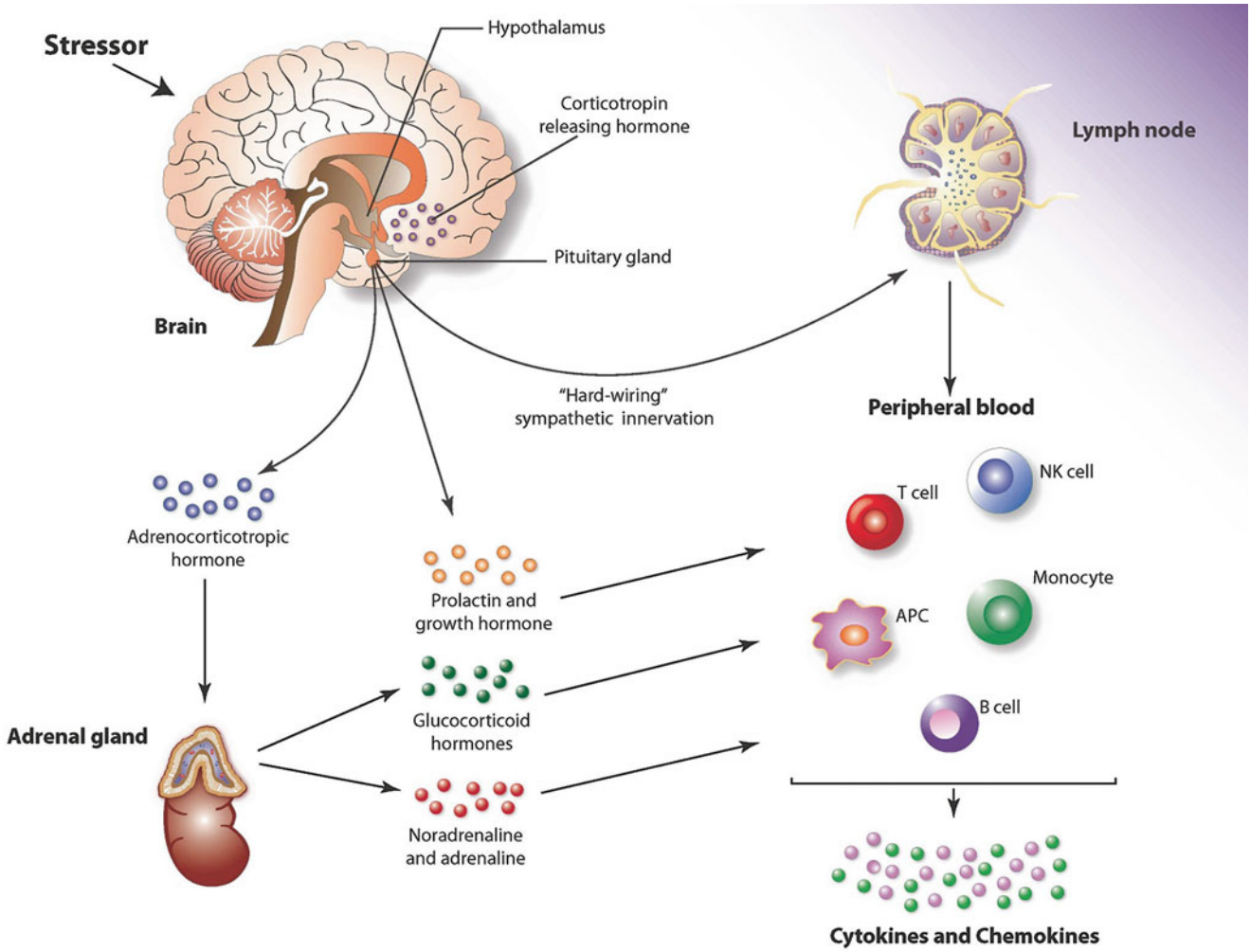

FIGURE 30.6. Modulation of the hormone response by stress and adverse life events. Activation of the hypothalamic–pituitary–adrenal (*HPA*) axis and the sympathetic nervous system results in release of glucocorticoids and catecholamines that modulate the function of the immune system. Immune alterations have been described in neurodevelopmental disorders such as schizophrenia and autism.

neuropsychiatric disorders (604–607), the effects of maternal stress on the HPA axis in rodent models should be taken cautiously, as the nature of the stressors, the duration of the stress, the intensity and persistence of the stressor, and the immune compartments may differ between humans and preclinical assays (608).

The molecular mechanisms through which prenatal adverse life events induce these phenotypic changes in the offspring remain unclear (548, 549, 604, 609, 610). One explanation has been suggested to be related to the enzyme 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2) (611), which protects the fetus by metabolizing the cortisol into the inactive form cortisone (612–614). Thus, exposure of rats to acute stress increased the activity of 11β-HSD2 (611), whereas no change was observed 6 days after exposure to chronic stress (611). Importantly, although there is a placental barrier preventing maternal cortisol from crossing into the fetus, it has been shown that increased maternal HPA-axis activity increases the expression of fetal and placental CRF (615).

Hypercortisolism is a common trait seen in depression, anxiety, and substance abuse disorders, due to excessive CRF receptor activation on the HPA axis (548, 616). Several studies have shown that prenatal dexamethasone exposure (a potent glucocorticoid drug with immunosuppressant properties) has similar effects in the offspring than those induced by maternal stress during pregnancy (549, 617, 618). Interestingly, these effects are prevented by corticosterone replacement (619), which supports the notion that CRF receptor and glucocorticoid receptor antagonists may serve to reduce HPA axis activity (620–624). Clinical trials with CRF receptor antagonists as new potential drugs to treat anxiety and other psychiatric disorders are currently being conducted (548).

In addition to maternal adverse life events during pregnancy, postnatal events may also modify brain plasticity and HPA axis (549). Consequently, early life stress has been shown to disrupt the homeostatic mechanisms that regulate the HPA axis, leading

to alterations in mood and cognition (625, 626). Some of the potential mechanisms responsible for these alterations include upregulation of arginine-vasopressin expression due to hypomethylation of a key regulatory region of this gene, an epigenetic modification that was reversed by administration of a vasopressin V_{1B} receptor antagonist (627). Postnatal events such as maternal care also modulate the relationship between prenatal adverse life events and alterations in the adult offspring (628). Together, these findings suggest in utero and early life events as possible therapeutic targets for psychiatric disorders.

30.19. Cytokines and Other Immune-Response Mediators

Cytokines are small peptides that were originally described as immune modulators (629) but have recently been shown to affect a diverse array of functions in the CNS (630–635). While it is clear that genetics plays an important role in the etiology of schizophrenia (636–640), the molecular mechanisms of transmission are complex as shown by demographic studies of familial segregations and monozygotic twins. Thus, these studies demonstrate that the risk for both genetically identical twins to develop schizophrenia is nearly 50% (641–644). Such results demonstrate an important contribution of environmental factors in the development of this complex disease. Importantly, epidemiological studies suggest that maternal environmental factors during pregnancy, such as infection (virus, bacteria and protozoa) (645–652), and severe adverse life events such as famine (653), war (654, 655), and death or illness in a first-degree relative (656) increase the risk of schizophrenia in the offspring. Recent findings in mouse models (657–660) and schizophrenia patients (646, 661) suggest that cytokines such as TNF-α, IL-1β, IL-6, IL-8, and IL-10 are involved, at least in part, in the pathophysiology of schizophrenia (see Fig. 30.6). A better understanding of the mechanisms of cross talk between the maternal and fetal immune systems (601, 662), as well as its implications in neurodevelopment, may help in discovering new targets to prevent the onset of schizophrenia and other neurodevelopmental psychiatric disorders (601, 662–667).

30.20. Epigenetic Targets

The completion of the sequencing of the human genome is viewed as an important milestone (668, 669). However, the primary sequence represents only the beginning of our understanding of how the genetic information is stored and read. In eukaryotic cells, in contrast to prokaryotes, the DNA is packaged in the form of a nucleoprotein complex called chromatin. The nucleosome is the basic repeating structural unit of chromatin, which contains 147 base pairs of DNA wrapped twice around an octamer of two copies of each core histone protein (H2A, H2B, H3, and H4). Histones are deeply evolutionarily conserved proteins with a globular domain and a flexible amino-terminal tail (670–672). The status of chromatin organization, and hence open or closed states of chromatin and DNA accessibility, depends on the so-called "epigenetic" modifications that fall into two main categories: DNA methylation and histone modifications (670, 671, 673–676). This epigenetic information has been shown to be fundamental during embryonic development and tissue-specific cellular differentiation (677, 678). Recent studies also suggest that epigenetic modifications might constitute a new template for psychiatric interventions.

30.20.1. DNA Methylation

DNA methylation is an epigenetic mark often associated with stable variations in gene expression that consists of the addition of a methyl group to the C5 position of cytosine at CpG dinucleotides (see Fig. 30.7). Most of the methylations occur outside of CpG islands, which are regions of DNA containing a high GC content (>55%) (679). They co-localize with approximately 60% of all promoters and are largely free of DNA methylation. Only a small proportion of these CpG islands becomes methylated during development, particularly within genomic regions that are cell-type specific. Methylation of DNA is catalyzed by a family of DNA methyltransferases (DNMTs): DNMT1, DNMT2, DNMT3A, and DNMT3B. DNMT3L stimulates the DNA methylation activity of DNMT3A and DNMT3B (680). During embryonic development, DNMTs are differentially expressed, and their spatiotemporal distribution has been suggested to play an important role in neurogenesis, neuronal maturation, and memory formation (681–684). These and other findings suggest that methylation of cytosines in CpG sites influences normal physiology and neuropsychiatric disorders.

GABA-ergic deficits have been proposed to play a fundamental role in pathophysiological conditions such as schizophrenia and bipolar disorder (685). In certain populations of these patients, vulnerability genes that include *GAD67*, *Reelin*, and *GAT1* have been shown to be downregulated in specific populations of telencephalic GABA-ergic neurons (686–688), which correlates with hypermethylation of the corresponding promoters (689–691). In rodent models, it has also been suggested that chronic treatment with clinically relevant doses of clozapine and sulpiride, but not haloperidol or olanzapine, induces dose-dependent

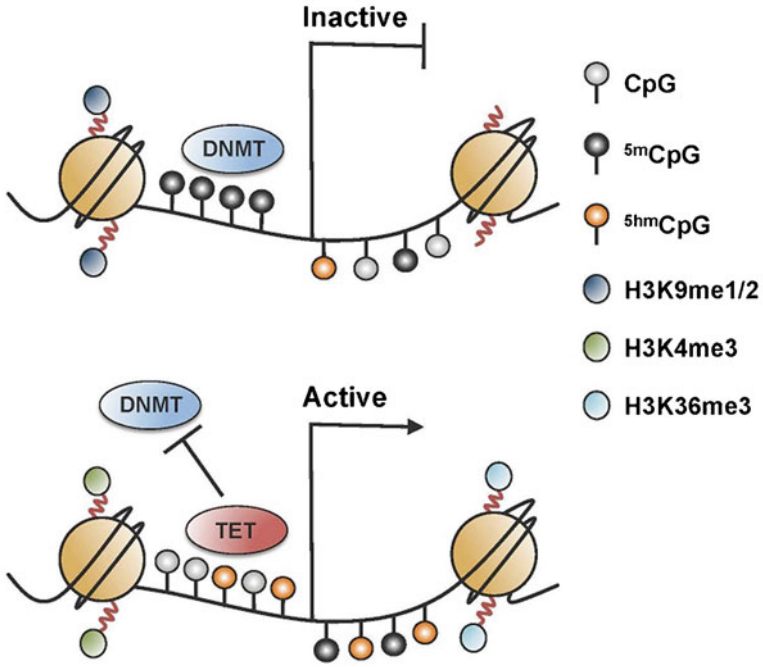

FIGURE 30.7. Mechanisms of gene expression control by DNA methylation. This schematic represents the association of DNA methylation at promoter regions with gene expression. The epigenetic mark 5-methylcytosine (5-mC), which is established by DNA methyltransferases (*DNMTs*) preferentially at CpG dinucleotides, is generally associated with gene expression and has long been regarded as a stable, highly heritable mark. Recent findings suggest that the oxidation of 5-mC to 5-hydroxymethylcytosine (5-hmC) by ten-eleven translocase (TET) proteins may relieve the repressive effects of 5-mC. Additionally, TET binding may prevent access to DNMTs, further contributing to the maintenance of an unmethylated promoter.

cortical and striatal demethylation at *Reelin* and *GAD67* promoters (692). Moreover, *DNMT1* mRNA expression is selectively upregulated in telencephalic GABA-ergic interneurons of schizophrenia patients (693, 694), with appears to be a consistent finding associated with schizophrenia morbidity. In peripheral blood lymphocytes, both *DNMT1* and *DNMT3A* mRNA expression is increased in schizophrenic patients, and these alterations remain unaffected by antipsychotic treatment (695).

As discussed above, environmental events early in life can induce long-lasting changes in neurophysiology and behavior. In postmortem hippocampus of suicide victims with a history of childhood abuse, suicide victims with no childhood abuse, and controls, recent findings suggest increased CpG methylation at the neuron-specific glucocorticoid receptor (*NR3C1*) gene promoter in samples from abused suicide victims (696). These findings are further supported by additional data in rat mothers with increased pup licking, grooming, and arched-back nursing. Thus, offspring of mothers that showed high levels of mother-pup contact exhibited decreased levels of DNA methylation at the glucocorticoid receptor gene promoter in the hippocampus (697). Environmental stressors during postnatal brain maturation in combination with genetic factors also induce behavioral abnormalities, dopaminergic disturbances, and distinct influence of glucocorticoids on the CpG sites inside the island of the *tyrosine hydroxylase* genes between mesocortical and mesolimbic dopaminergic projections in mice (698). These data suggest that environmental experiences early in life result in epigenetic alterations that ultimately affect behavior.

DNA methylation has also been involved in mechanisms related to cocaine reward. Thus, self-administration of cocaine induces upregulation of *Dnmt3a*, but not *Dnmt1* or *Dnmt3b*, in NAc of mice after 28 days of withdrawal (699). At a subcellular level, chronic cocaine increased thin dendritic spines on NAc neurons, and intra-NAc infusion of the RG108, a potent non-nucleoside DNMT inhibitor, blocks cocaine's action on dendritic spine density (699), which points toward DNA methylation as a mechanism that controls emotional behavior related to drug addiction.

An unusual DNA nucleotide, 5-hydroxymethylcytosine (5-hmc), was detected while comparing the levels of 5-methylcytosine (5-mC) in cerebellar Purkinje neurons (700). In parallel, another group identified the ten-eleven translocase (TET) proteins that hydroxylate 5-mC to form 5-hmC (701). There is now considerable interest in this field as hydroxylation of 5-mC is likely the first step in the mechanism through which DNA methylation is reversed (see Fig. 30.7). Although several studies suggest an important role of alterations in DNA methylation as potentially involved in schizophrenia, the used experimental platforms do not distinguish 5-mC and 5-hmC. Further work is therefore necessary to define the role, if any, of 5-mC to 5-hmC conversion in schizophrenia.

During the past 3 years, two additional cytosine variants were identified in the mammalian genome: 5-formylcytosine and 5-carboxylcytosine. These newly revealed DNA base modifications immediately drew broad attention from the research community and have been extensively reviewed (702, 703). Understanding the dynamics of these modifications in living biological systems could lead to novel treatments for a number of psychiatric conditions.

30.20.2. Histone Deacetylases (HDACs)

Covalent modifications at the N-terminal tail of histones correlate with open or closed states of chromatin depending on the type of modification. Thus, acetylation of histone H3 (H3ac) and acetylation of histone H4 (H4ac) are modifications that create a more open chromatin architecture (704). Histone methylation, on the contrary, correlates with either transcriptional activation, such as methylation of lysine 4 on histone H3 (H3K4me) and methylation of lysine 36 on histone H3 (H3K36me), or repression, such as methylation of lysine 9 on histone H3 (H3K9me) and methylation of lysine 27 on histone H3 (H3K27me), depending on the histone and amino acid residue being methylated. Histone acetylation is catalyzed by histone acetyltransferases (HATs), and this modification can be reversed by the enzymatic action of histone deacetylases (HDACs) (see Fig. 30.8). Members of the HDAC family fall into four different phylogenetic classes: class I (HDAC1, 2, 3, and 8), class II (HDAC4, 5, 6, 7, 9, and 10), class III (SIR2 family of NAD^+-dependent HDACs), and class IV (HDAC11). Class I and II (Zn-dependent) and class III (NAD^+-dependent) show different distribution and are expressed among distinct cell types, including neurons, oligodendrocytes, and astrocytes (705). Recent findings in preclinical models and clinical studies suggest that HDAC inhibitors might emerge as a new target for the treatment of cognitive disorders.

In animal models, HDAC inhibitors, such as sodium butyrate, valproate, MS-275, suberoylanilide hydroxamic acid (SAHA), facilitate cognitive enhancement and memory formation (706–710). Importantly, results in rodent models suggest that HDAC2 may serve as new target for HDAC inhibitors to facilitate memory formation. Thus, neuron-specific overexpression of HDAC2, but not HDAC1, decreased dendritic spine density and memory formation, whereas HDAC2 knockout mice showed increased synaptic number and memory facilitation (711). The role of HDAC2 was further supported with findings demonstrating that HDAC inhibitors fail to facilitate memory formation in HDAC2 knockout mice (711).

In schizophrenia, some (712–717), but not all (718, 719), clinical studies suggest that HDAC inhibitors such as valproate are efficacious when given in combination with atypical antipsychotic drugs. Recent findings suggest an epigenetic mechanism through which chronic antipsychotic treatment induces repressive histone modifications at the *mGlu2* promoter in mouse frontal cortex (720). Similar findings were observed in postmortem frontal cortex of treated, but not untreated, schizophrenic subjects, suggesting that this epigenetic modification represents a consequence of antipsychotic treatment and not an alteration in schizophrenia patients (720). Chronic treatment with the atypical antipsychotic clozapine also induced selective upregulation

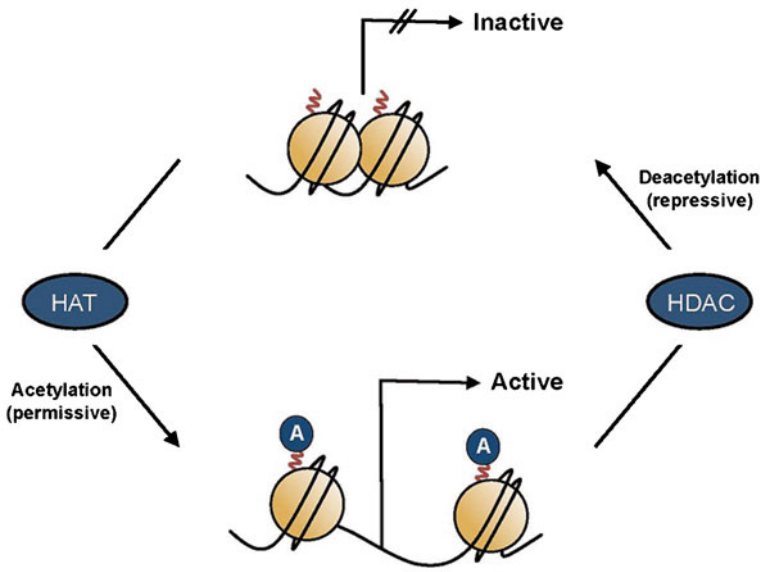

FIGURE 30.8. Model of the mechanisms underlying chromatin remodeling. This schematic presents a model of histone modifications: acetylation and deacetylation at histone N-terminal tails. Histone acetylation is associated with opening the nucleosome to allow binding of the transcriptional complex. Acetylation is catalyzed by histone acetyltransferases (*HATs*), and reversed by histone deacetylases (*HDACs*).

of expression of HDAC2, an effect that was associated with a serotonin 5-HT_{2A} receptor-dependent regulation of *HDAC2* promoter transcriptional activity (720), and increased binding of HDAC2 to the promoter region of the *mGlu2* gene. Viral-mediated overexpression of HDAC2 in mouse frontal cortex decreased the expression of *mGlu2* and its electrophysiological properties, which ultimately augmented schizophrenia-like behavior and cognitive deficits in mice. Correspondingly, peripheral and intra-frontal cortex administration of HDAC inhibitors prevented the repressive histone modifications induced at the *mGlu2* promoter by atypical antipsychotics, and improved their therapeutic-like effects (720, 721). These findings offer perspectives for the rational design of HDAC2 inhibitors as a therapeutic strategy for schizophrenia (722, 723).

Using chronic stress as a mouse model of depression and chronic treatment with imipramine as a mouse model of antidepressant action, it has been demonstrated that chronic imipramine treatment induces selective downregulation of *HDAC5* mRNA in the hippocampus (561). Furthermore, viral-mediated overexpression of HDAC5 in the hippocampus reversed the antidepressant-like behavioral effects induced by chronic treatment with imipramine (561), providing a new insight into the underlying molecular mechanisms of depression and antidepressant action.

Chromatin remodeling has also been proposed as an important mechanism controlling cocaine-induced plasticity. Prolonged blockade of HDAC1, but not HDAC2 or HDAC3, in NAc of mice increased global levels of histone acetylation, induced repressive histone methylation, and reversed the behavioral changes induced by cocaine (724). These effects were mediated through a molecular mechanism that required repressive histone modifications at the promoter regions of *Gabra1* and *Gabra2* genes in the NAc (724), which correspond with $GABA_A$ receptor subunits. Repeated cocaine administration also reduced global levels of H3K9me2 in the NAc, an epigenetic change that was mediated through the repression of the lysine dimethyltransferase G9a (725). This repression of G9a and H3K9me2 after repeated cocaine administration promotes cocaine preference through the transcriptional activation of genes that had previously been shown to regulate aberrant forms of dendritic plasticity (725).

Class II HDACs (HDAC4, 5, 6, 7, 9, and 10) shuttle between nucleus and cytoplasm through calcium-dependent phosphorylation, which depends on synaptic release of excitatory neurotransmitters (726). Recent studies have shown that nuclear export of HDAC4 induced by glutamatergic input represses a group of genes related to synaptic plasticity in cortical neurons, and that forebrain-specific lack of HDAC4 results in impairment of memory formation (727, 728).

HDAC6 is a microtubule-associated cytoplasmic protein with two deacetylase domains (729, 730). In a *Drosophila melanogaster* model of the neurodegenerative disorder spinobulbar muscular atrophy, HDAC6 enhances the autophagy pathway through interaction with polyubiquitinated proteins when the ubiquitin-proteasome system is unpaired (731), suggesting that HDAC6 may represent a new target for the treatment of neurodegenerative disorders such as Alzheimer's disease, Huntington's disease, and amyotrophic lateral sclerosis. It has also been suggested that HDAC6 knockout mice exhibit less anxiety-like and depression-like behaviors (732, 733).

Based on these findings, HDAC inhibitors may emerge as a valuable treatment strategy for schizophrenia, depression, drug abuse, and other psychiatric disorders. From a more general perspective, these studies provide insights into the role that epigenetic factors may play in neuropsychiatric disorders and their treatment. Further investigation is necessary to elucidate the mechanisms underlying the modulation of histone modifications and DNA methylation in order to develop novel approaches for the treatment of chronic psychiatric diseases.

30.21. Apoptotic Pathways

In metazoans, cell decisions must be strictly controlled by balancing cell proliferation and cell death (734, 735). The term apoptosis, also called programmed cell death, is defined by hallmarks such as mitochondrial changes that include collapse of the transmembrane electrochemical potential and release of cytochrome c to the cytosol, activation of caspases, chromatin condensation, activation of endonucleases and internucleosomal DNA cleavage, fragmentation of the nucleus, and plasma membrane blebbing associated with formation of apoptotic bodies (736–738). Recent findings suggest that the signaling pathways controlling metabolism and apoptosis are intertwined, which emphasizes the dual nature of several core apoptotic proteins. In the CNS, classical apoptosis can be initiated through the extrinsic (e.g., apoptosis-1 protein [Fas] death receptor) and intrinsic (e.g., mitochondrial proteins) pathways, which ultimately converge to the activation of caspases (e.g., caspases-3/7) with the final cleavage of downstream cellular substrates (739–742). It has also been suggested that apoptotic regulators, such as FADD, cytochrome c, $FLIP_L$, and Bcl-2, are distinctly modulated by opiate drugs in the prefrontal cortex of short- and long-term human opiate abusers (743). These neurochemical adaptations may play a major role in the development of tolerance and relapse in human addicts. Similar findings were observed in the cerebral cortex of human cocaine addicts and cocaine-treated rats (744). These findings further support the hypothesis that the so-called apoptotic proteins also induce non-apoptotic (neuroplastic) actions in the CNS, which illustrates a very challenging and important field of study for years to come.

30.22. Mitochondrial Abnormalities

Mitochondria play a key role in cellular energy metabolism. However, they are also involved in amino acid, lipid and steroid metabolism, as well as in modulation of cellular calcium levels, production of free radicals and regulation of apoptosis (745–750). Thus, mitochondrial dysfunction not only affects energy production, but also impairs other cellular events. Based on this, emerging evidence suggests that impaired mitochondrial function may disrupt neuronal plasticity. It is clearly established that mood and psychotic disorders are not classic mitochondrial disorders (751). However, recent findings support that mitochondria may represent a new target for novel therapeutic approaches. Two recent studies suggest that mitochondria-regulated caspase activation modulates synaptic plasticity (752, 753). An altered mitochondrial function has also been shown in cells from patients with mood disorders and bipolar disorders. Mitochondria-related genes were globally downregulated in postmortem human brains of patients with bipolar disorder (754–756). In psychotic disorders, some studies have suggested associations between variations in mitochondrial DNA (mtDNA) and schizophrenia (757–759). Mitofilin, a mitochondrial inner membrane protein (760), has been shown to function as a mediator of the mitochondrial function of DISC1 (761). Thus, DISC1 plays an essential role for mitochondrial function together with a mitochondrial interacting partner Mitofilin (761). These findings suggest that the ability to modulate mitochondrial function may have an important role in regulating complex brain functions such as cognition and perception.

30.23. Future Directions

One of the main concerns in psychiatry is that biologists have been unable to find genetic or neurobiological evidence to support the classification of complex mental disorders into separate categories. The latest edition of the DSM-5 (4), like the preceding editions, groups disorders into discrete categories, such as schizophrenia, major depressive disorder and bipolar disorder. A growing line of research moves away from the "category" approach and towards the "dimensional" approach, in which mental-health conditions lie along a spectrum that has partly overlapping causes and symptoms (762, 763). The therapeutic drugs currently available are designed only to treat the symptoms of psychiatric conditions, and not the underlying causes of the disease. Because of this, psychiatric disorders generally remain incurable illnesses, and the treatment of their symptoms typically lasts for months or years, sometimes continues for life. The development of translational methods in animal models and heterologous systems may help in discovering therapeutic targets for not only treatment but also prevention of psychiatric conditions.

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31
Use of Laboratory in Psychiatry

Inna D'Empaire, M.D., Sheldon H. Preskorn, M.D., and Matthew Macaluso, D.O.

Abstract Laboratory assessment is an important compliment to the clinical interview and physical examination in establishing the diagnosis and implementing/monitoring treatment. To illustrate the clinical relevance of laboratory use a case example is presented throughout the chapter with the purpose of discussing laboratory use as an aid in establishing the diagnosis and general health status by ruling out an underlying comorbid medical condition and monitoring treatment adequacy and safety. Skillful use and interpretation of laboratory tests should aid in identification of an underlying condition and lead to a better understanding of the disease process.

Keywords Use of laboratory in psychiatry • Minimum laboratory tests • Lab use in comorbid medical conditions • Therapeutic drug monitoring • Treatment adequacy • Treatment safety • Biological effects of drugs

31.1. Use of Laboratory in Psychiatry

The goal of this chapter is to provide a practical overview and explain a current perspective on the use of the laboratory in psychiatry (1, 2). The underlying theme of this chapter is that laboratory assessment is an important compliment to the clinical interview and physical examination in establishing the diagnosis and implementing/monitoring treatment.

This chapter is based on the principle that psychiatry is a specialty within the general field of medicine. As in every medical specialty, the laboratory serves two important roles in managing a patient with psychiatric illness.

These roles are:

- aid in establishing the diagnosis and general health status by ruling out an underlying comorbid medical condition;
- monitoring treatment adequacy and safety.

Even though each laboratory test is an objective and measurable parameter by definition, the laboratory serves only an auxiliary role in diagnosis and treatment. Nevertheless, the laboratory work-up is an important source of information which compliments the objective findings derived from a detailed medical history and a comprehensive physical examination. Each

I. D'Empaire, M.D. (✉)
Associate Professor, Director of Consultation-Liaison Service, Department of Psychiatry and Behavioral Sciences, University of Kansas School of Medicine-Wichita, and Clinical Research Institute, Wichita, KS, USA
e-mail: idempaire@kumc.edu

S.H. Preskorn, M.D.
Professor, Department of Psychiatry and Behavioral Sciences, University of Kansas School of Medicine-Wichita, Wichita, KS, USA
e-mail: spreskorn@kumc.edu

M. Macaluso, D.O.
Assistant Professor, Department of Psychiatry and Behavioral Sciences, University of Kansas School of Medicine-Wichita, Wichita, KS, USA
e-mail: mmacaluso@kumc.edu

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TABLE 31.1 Outline of the laboratory use in psychiatry.

Use to establish the diagnosis	(a) Minimum laboratory test needed to assess general health (b) Specific additional tests needed to assess comorbid medical conditions (c) Special cases with specific laboratory assessments: 1. Dementia 2. Substance abuse or dependence (d) Special laboratory tests: 1. Computerized tomography 2. Magnetic resonance imaging 3. Functional magnetic resonance imaging
Use to monitor treatment adequacy and safety	(a) Monitor drug levels 1. Antidepressants 2. Antipsychotics 3. Mood stabilizers (b) Monitoring the biological effects of drugs

diagnostic test should be applied and interpreted within the context of the particular clinical scenario at hand. In this chapter, summary tables discussing a variety of laboratory tests applicable to psychiatry will be provided, including the outline for the chapter (Table 31.1). To illustrate the clinical relevance of this chapter, it begins with a case example that will be continued throughout the remainder of the chapter:

31.1.1. Clinical Vignette

Mrs. X, a 47 year old Caucasian woman with metastatic malignant melanoma, who had just completed her 4th week of adjuvant chemotherapy treatment with interferon α. She had a history of one psychiatric hospitalization and was taking lithium and sertraline. During the past 2 weeks she had been feeling fatigued, nauseated and unable to maintain adequate oral intake. Her family noted slurring of speech, listlessness, problems with balance and increased confusion to the point that she has been requesting to take multiple baths during the day without recollection. The patient complained of diarrhea, coarse tremor, worsening of balance and coordination, and blurred vision. She decided to stop psychiatric medications due increasing nausea, vomiting, diarrhea, and diffuse abdominal pain. She presented to the local emergency room one week later for an evaluation of persistent confusion.

Questions to consider prior to laboratory work-up:

- What is the working diagnosis?
- What laboratory tests might help in evaluating the diagnosis and establishing the patient's general health?

31.2. Laboratory Use to Establish the Diagnosis

Each clinician is faced with a daily challenge of using appropriate laboratory tests to support and clarify their diagnostic formulation. Patients describe various signs and symptoms. The clinician frequently needs to group and sometimes regroup them to formulate a working diagnosis or hypothesis and the relevant differential diagnoses.

Knowledgeable and skillful use of laboratory tests can help establish a logical connection from the interpretation of unrelated signs and symptoms to recognition of a known syndrome to an understanding of the underlying pathophysiology and etiology and finally to effective treatment.

Mrs. X presented with a sudden onset of uncharacteristic confusion, fluctuating level of consciousness and perceptual disorganization. This constellation represents an acute delirium. Additional symptoms such as slurred speech, listlessness, problems with balance and coordination, blurred vision and coarse tremor should lead to thinking about possible drug-induced central nervous system (CNS) toxicity.

Further history revealed that this patient had recently been treated with lithium 300 mg twice daily and sertraline 100 mg daily. Mrs. X had been diligently taking lithium for the past 10 years without experiencing any adverse effects. This medication had been started as a result of an earlier, single psychiatric hospitalization due to agitated behavior interpreted as a manic episode. Given this history, lithium toxicity should be considered in the differential diagnosis since it can produce many of the signs and symptoms that this patient had. If that was the case, then discontinuation of the drug should lead to the resolution of the delirium. This clinical case can also be viewed from the system-based approach and described utilizing stages of diagnostic sophistication presented in Table 31.2.

TABLE 31.2 Levels of diagnostic sophistication.

Stages	Definition	Example	Laboratory test
Symptomatic	Single symptom	Confusion	Minimum data set
Syndromic	Cluster of symptoms and/or signs	Delirium	Additional tests
Pathophysiological	Knowledge of physiological disturbance	Dysfunction of neural circuits in cortical and subcortical regions of the brain	Neuroimaging
Etiological	Knowledge of causative agent	Lithium neurotoxicity	Specific laboratory assessments

31.3. Minimum Laboratory Tests Needed to Establish General Health

As the reader will recall, Mrs. X had just completed a course of interferon treatment which can produce a number of clinically significant adverse effects including many neuropsychiatric symptoms such as: depression, anxiety, fatigue, anorexia, visual disturbances and increased irritability. Parenthetically, researchers are studying the effects of interferon in animals to gain insight into possible neural mechanisms underlying depressive disorders in man.

As the case of Mrs. X illustrates, additional history and collateral information can provide many necessary details causing the treating physician to order laboratory tests to confirm or reject possible explanations. Table 31.3 summarizes the "minimum data set" to be considered at the time of the initial patient encounter to narrow the diagnostic impression, help with the differential diagnoses and support the history.

Mrs. X presented with the symptoms of nausea and vomiting, decreased oral intake and fatigue. Physical exam findings were consistent with dehydration (dry, pale skin and mucous membranes), CNS impairment (slurred speech, blurred vision, ataxia, unstable gait, impaired coordination) and liver toxicity (yellowish sclera). Therefore, vital signs, complete blood count with differential, basic metabolic panel, liver function tests and urine analysis were ordered.

Mrs. X later reported that she tried using over-the-counter (OTC) remedies to help relieve headache and fatigue and had a history of using marijuana to increase appetite during the first few days of interferon treatment. She had been treated with lithium and interferon, both of which can interfere with thyroid function. On the other hand, patients with hypothyroidism can present with symptoms of depression. Given the history of prescription, OTC and "recreational" drug use in this case, ordering thyroid stimulating hormone level and urine drug screen (UDS) would therefore be appropriate and desirable. Parenthetically, a good clinical practice rule is to obtain a urine pregnancy test in females of childbearing potential especially in psychiatry because most psychiatric medications have category C and D listing for use during pregnancy.

31.4. Additional Tests Needed to Assess Comorbid Medical Conditions

Beyond the minimum data set discussed above, a thorough medical history will frequently suggest the need for additional specific laboratory testing to further optimally assess the patient and assist with treatment and planning. History of liver, kidney, or heart disease, hypothyroidism, tuberculosis, or other diseases mandates certain laboratory tests regardless of the patient's psychiatric presentation. Table 31.4 provides the set of additional laboratory tests which should be considered based on the previous laboratory test results and the specific medical history of the patient. Even though comprehensive laboratory evaluations are originally and ideally supported by the working hypothesis, which can change on an hourly or daily basis, the clinician is frequently faced with everyday challenges of sorting through complex scenarios.

Several questions should be considered when ordering specific diagnostic tests:

- What is the diagnostic value of the test?
- What is the specificity and the sensitivity of each test in this particular situation?
- What is the probability of obtaining the desired information?
- What is the risk versus benefit ratio of the test or diagnostic procedure?
- Is there any personal discomfort (physical and emotional) associated with a test?
- What is the cost of the test versus its potential cost savings?

The judgment of whether a physical complaint is attributable to an underlying general medical condition is a difficult one. It should be based on all reasonable sources of information, including the patient's past medical history, current presentation, physical examination and laboratory findings. The cost of possible negative laboratory tests must be balanced against the risk of not identifying a potentially reversible underlying general medical condition. The physical examination, including detailed neurological examination, should not be neglected and ought to be performed prior to ordering a laboratory evaluation.

TABLE 31.3 Minimum laboratory tests needed to assess general health.

Basic metabolic panel
Complete blood count with differential
Liver function tests
Thyroid stimulating hormone (TSH)
Urinalysis
Urine drug screen (UDS)
Urine pregnancy test in females of childbearing potential
Vital signs

TABLE 31.4 Additional tests specifically needed to assess comorbid medical conditions.

Additional tests (as indicated)	**Example of comorbid medical condition**
Ammonia level	Liver failure
Antinuclear antibody	Systemic lupus erythematosus
Arterial blood gas	Pulmonary embolism
B12/folate level	Peripheral neuropathy
Blood culture	Sepsis
Chest X-ray	Tuberculosis
Drug of abuse confirmation test: gas chromatograph/mass spectrometer (GC/SM)	Cough syrup use
Electroencephalography, evoked potentials	Seizure disorder
Erythrocyte sedimentation rate and Rheumatoid factor	Rheumatoid arthritis
Hepatitis panel	Hepatitis C
Human immunodeficiency virus	Lymphoma
Lead level	Peripheral neuropathy
Liver function tests	Hepatitis
Lumbar puncture with cerebrospinal fluid studies	Meningitis
Neuroimaging: CT, MRI with or without contrast	Space occupying lesion
Polysomnography	Insomnia
Serum ceruloplasmin level	Wilson's disease
Serum osmolality	Diabetic ketoacidosis
Serum pregnancy test	Anemia
Skin tests for tuberculosis	HIV/AIDS
Stool: occult blood	GI tract ulcer/malignancy
Urine: porphyrins, osmolality	Acute intermittent porphyria

In this regard, Mrs. X was on immunosuppressant therapy and complained of nausea, vomiting, diarrhea and abdominal pain, which can be due to lithium toxicity. Taking into consideration the patient's history of metastatic malignant melanoma and the fact that the results from the previously ordered tests were consistent with microcytic anemia, elevated liver enzymes, elevated temperature and a urine drug screen positive for opioids and methamphetamines the differential diagnoses list can easily expand. These test results could be explained by detailed questioning of the patient: for example, the positive hepatitis C could be due to the fact that this patient had a history of having received a blood transfusion in her 20s after a motor vehicle accident. The positive urinary drug screen (UDS) could be explained by history indicating consumption of a poppy seed bagel for breakfast in addition to over-the-counter cough syrup prior to the admission which could be the cause of the positive UDS.

Nevertheless, hepatitis panel, HIV testing and drug of abuse confirmation tests (GC/MS gas chromatography/mass spectrometry) would be appropriate to further clarify the diagnosis, and determine whether an open discussion about illicit drug use would be appropriate (3).

31.5. Special Cases with Specific Laboratory Assessments

31.5.1. Dementia

Specific cost-effective test batteries can be applied in clinical practice to patients presenting with signs and symptoms consistent with certain psychiatric syndromes, such as dementia and substance abuse or dependence. In clinical practice, these syndromes often coexist and add an interesting complexity. Usually, the first step in the work-up of a patient presenting with

TABLE 31.5 Special cases with specific laboratory assessments: dementia.

Elderly psychiatric patients
Screening tests:
Complete blood count with differential cell type count
Erythrocyte sedimentation rate
Liver function tests
Serological test for syphilis (fluorescent treponemal antibody absorption)
Thyroid function tests
Urinalysis
Vitamin B12 and folate level determinations
Complete biochemical profile: including serum electrolyte determinations (sodium, potassium, bicarbonate), blood urea nitrogen level, serum creatinine level, serum calcium and phosphorus levels, and blood glucose level
Other tests:
Chest radiography
Computed tomography (CT) head scan
Electrocardiography
Lumbar puncture, if indicated
Magnetic resonance imaging (MRI) head scan
Positron emission tomography (PET)
Single photon emission computed tomography (SPECT)
Test selected for individual patients:
Antinuclear antibody
Arterial blood gases
Human immunodeficiency virus (HIV) antibodies, including Rapid HIV testing return
Homocysteine level
Serum copper and ceruloplasmin for Wilson's disease
Urine drug screen, heavy metals screen, blood alcohol level

a new onset dementia or even an acute exacerbation of chronic dementia is to determine whether an underlying reversible and treatable general medical condition is present. Table 31.5 lists specific test batteries, which are aimed at identifying dementias associated with anemia, neurosyphilis, major organ failure (hepatic, renal), hypothyroidism, vitamin deficiency, normal pressure hydrocephalus or/and space occupying lesion.

The case of Mrs. X illustrates the use of laboratory assessment in the field of psychiatry as a subspecialty of medicine. For the purposes of the discussion, let us assume that Mrs. X was diagnosed with HIV 10 years ago and complained of being forgetful, misplacing things and exhibited difficulty balancing her bank accounts for the past 6–8 months. She also reported a family history of Alzheimer's and Parkinson's disease. Additional laboratory tests and history would put the case and its evaluation into a different diagnostic perspective requiring consideration of HIV-associated dementia and justifying the request for HIV testing.

As a general rule, elderly patients are more likely to benefit from additional laboratory work-up compared to younger people (4, 5). High rates of unrecognized medical illness in patients with psychiatric presentations (6) and history consistent with poor medical follow up can also warrant increased use of laboratory testing. These tests can be helpful in the following groups (7, 8):

Chest X-ray is useful in:

- elderly;
- patients with alcohol and drug-related problems;
- patients with cognitive impairment.

Chest X-Ray is useful in the elderly to rule out community acquired pneumonia. In the modified history of Mrs. X given above, a chest X-ray would be helpful in establishing whether Mrs. X has tuberculosis and/or pneumocystis carinii pneumonia (PCP) versus disease (metastatic melanoma) progression in an immunocompromised patient.

For the purposes of discussion, assume Mrs. X reported occasional drinking with poor nutritional intake and a recent onset of non-productive cough. Chest X-ray would be a helpful diagnostic tool to identify aspiration pneumonia.

Electrocardiography is helpful in patients who:

- have cardiac symptoms/signs;
- are over 50 years old;
- have pre-existing cardiac condition;
- are being treated with drugs known to prolong cardiac conduction (e.g., QT interval).

TABLE 31.6 Special cases with specific laboratory assessments: substance abuse or dependence.

Blood alcohol level	Evidence of current intoxication
SGOT/AST	Elevation in alcohol induced hepatitis
SGPT/ALT	May return to normal in patients with advanced cirrhosis
LDH	
SGGT	Correlates with increased alcohol consumption
CDT	Found to be superior to SGGT in detecting heavy alcohol consumption
GC/MS	Confirmation test for drugs of abuse
Increased amylase	Pancreatitis
Pancytopenia, MCV >100	Bone marrow suppression
Decreased Albumin, vitamin B12, folate, MCV>100	Malnutrition
Increased prothrombin time, decreased BUN	Liver cirrhosis

SGOT—serum glutamic-oxaloacetic transaminase.
AST—aspartate transaminase.
SGPT—serum glutamic-pyruvic transaminase.
ALT—alanine transaminase.
LDH—lactate dehydrogenase.
SGGT—serum gamma-glutamyl transferase.
CDT—carbohydrate-deficient transferrin.
GC/MS—gas chromatograph/mass spectrometer.
MCV—mean corpuscular volume.
BUN—blood urea nitrogen.

31.5.2. Substance Abuse or Dependence

Laboratory plays an important role in the work-up of a patient presenting with possible substance abuse or dependence (9). UDS is probably one of the most frequently used tests when the substance abuse/dependence is suspected. The most common substances of abuse/dependence detected by the UDS include cocaine, amphetamine (including ecstasy), opiates, marijuana, and benzodiazepines (3).

Urine drug screen is a screening test designed to detect a wide range of potential substances of abuse, therefore, it frequently can be false positive due to cross-reactivity with other chemical compounds. Several medications such as bupropion, OTC Vicks® inhaler can produce false positive test for amphetamines, poppy seeds and some antibiotics (levofloxacin, ofloxacin) can cause false positive tests for opiates and diphenhydramine for tricyclics. A false positive UDS for the presence of drugs of abuse could result in unnecessary confrontation. In those cases when patients deny the use of illicit drugs despite a positive UDS, a confirmation test by gas chromatograph/mass spectrometer (GC/MS) can clarify the discrepancy.

In the case of Mrs. X, the screening UDS was positive for methamphetamine and opiates. However, the patient denied using those substances and the results were confirmed by the GC/MS test. If Mrs. X had refused the urine drug testing and if the reasons to test were sufficiently compelling hair, nails, saliva, or sweat could have been used as alternative biological specimens with the patient's permission. Since each laboratory is set up to detect certain levels of the questioned compound with preset threshold for each substance of interest, in order to increase the sensitivity of the test and the likelihood of detecting the illicit substance or determine the presence of prescribed medications the option of "no threshold" should be requested. Cocaine on the other hand is usually associated with illicit substance use unless the patient is able to offer a medical explanation for a positive test, such as cocaine use as a topical anesthetic in dental procedure, which by itself is rarely sufficient to produce a positive UDS.

Table 31.6 describes laboratory tests associated primarily with alcohol abuse. Fortunately, Mrs. X understood the danger of concomitant alcohol consumption and immunosuppressant therapy and was able to stop drinking with her family's support and intensive outpatient chemical dependency treatment prior to initiation of interferon treatment. Her serum gamma glutamyl transferase (SGGT) and carbohydrate-deficient transferrin (CDT) were within normal limits.

31.6. Neuroimaging

Recent advances in these procedures permit assessment of both structural and functional abnormalities in the brain. Computerized tomography (CT) (10) is widely used in the emergency rooms and is especially indicated for patients presenting with psychiatric symptoms if they belong to one of the categories described below:

- over 40 years old with no prior psychiatric history;
- first episode of psychosis, mania, or acute personality change;
- differential diagnosis of delirium or dementia;

Table 31.7 Electroencephalography.

Delirium	Diffuse slowing, Dropout of the dominant posterior rhythm.
Herpes simplex encephalitis	Periodic temporal spikes 2–3 per second and slow waves.
Hepatic and uremic encephalopathy	Triphasic waves
Subacute sclerosing panencephalitis, Creutzfeldt–Jakob disease	Periodic complexes

- rapid onset of neuropsychiatric symptoms;
- abnormal neurological examination;
- recent memory loss.

A CT scan of the head is used primarily to rule out hemorrhagic insult to the brain or space occupying lesion. Lumbar puncture should be considered in cases of acute mental status change and inconclusive neuroimaging studies. Major brain regions of interest to psychiatry and the field of neuroanatomy of higher cognitive functions include: orbital medial prefrontal complex, the amygdala, striatum, and thalamus (11–13). Magnetic resonance imaging (MRI), functional-MRI (14) and magnetic resonance spectroscopy (MRS) have the advantages of assessing both brain structural and functional status by using non-invasive techniques.

The following findings have been consistently demonstrated using various brain imaging techniques in either dementia or schizophrenia:

Dementia

- enlarged ventricles
- generalized versus focal atrophy
- decreased metabolism in parietal, frontal, and/or temporal areas
- evidence of vascular compromise
- hypoperfusion in posterior temporal-parietal regions in patients with Alzheimer's disease.

Schizophrenia

- decreased frontal lobe size
- reduced prefrontal metabolism
- enlarged ventricles (particularly frontal horns)
- high ventricle to brain ratio
- corpus callosum abnormalities
- dysfunction of dorsolateral prefrontal cortex

In the case of Mrs. X computerized tomography was used during her emergency room visit to rule out metastatic brain lesions as a source of increasing confusion.

If Mrs. X had failed to stop lithium and developed severe neurotoxicity, then electroencephalography (EEG) (15), another tool to measure brain physiological or functional status, could be used to monitor brain activity. EEG can be particularly helpful in the case of suspected seizure disorder, encephalitis, delirium, rapidly progressive dementia, or profound coma. However, there is a need for caution because the EEG reading can be misleading in the case of cerebral infarction or brain injury. Table 31.7 reflects most pertinent and consistent EEG findings.

31.7. Laboratory Use to Monitor Treatment Adequacy and Safety of Antidepressant and Antipsychotic Drugs

The following equation defines the three variables that determine the response to any drug (Table 31.8). Three variables determine individual response to any medication: 1) the affinity for and intrinsic activity of the drug at its site of action, 2) the concentration of the drug achieved at its site of action, and 3) the specific biology of the patient. It also provides the rationale underlying therapeutic drug monitoring (TDM). This equation can be viewed as an essential organizing principle for understanding the response of any patient to any specific single drug or combination drug regimen and is helpful in establishing a systematic and inclusive approach to each individual patient (16–20).

TABLE 31.8 Clinical response formula.

Clinical response		
Site of action	Drug concentration at site of action	Underlying biology of patient
Affinity for site	**A**bsorption	**G**enetics
Intrinsic activity at site	**D**istribution	**A**ge
	Metabolism	**D**isease
	Elimination	**E**nvironment

TDM in psychiatry can be used to accomplish several goals:

- assess compliance
- minimize adverse effects and toxicity
- enhance therapeutic response
- define the dose–response relationship in a population of patients or in a specific patient
- avoid drug–drug interactions
- shorten the length of stay
- improve the outcome
- minimize the cost of care
- avoid medico-legal problems

TDM can be used effectively to help differentiate between the early signs of toxicity versus worsening of an underlying condition and avoid increasing the dose in error, justify and objectively monitor prescribing higher than usual doses of certain drugs, and monitor use of medications which have a narrow therapeutic index. Standard antidepressant/antipsychotic registration trials generally fail to establish a correlation between an antidepressant/antipsychotic response and the plasma concentration due to poor signal-to-noise ratio. It has been well established that in a clinical trial the rule of thirds can be applied: one third of the patients would respond to the active compound, one third would respond to placebo, and one third do not respond sufficiently, therefore TDM is not well established for newer antidepressants/antipsychotic medications (51).

TDM can vary in terms of usefulness with a drug required for either safety or efficacy reasons to simply helpful in addressing matters such as adherence. Whether it is necessary rather than simply helpful, is determined by the following pharmacodynamic and pharmacokinetic characteristics of the drug:

- narrow therapeutic index
- insidious onset of toxicity
- multiple mechanisms of action
- large biological variability in drug levels
- delayed onset of action

TDM with antidepressant (21, 22) and antipsychotic medications (Table 31.9) can be beneficial when the patient is:

- taking a tricyclic antidepressant (23);
- experiencing an acute and serious medical illness;
- exhibiting a poor response;
- belongs to a special high risk population (e.g., children, elderly).

In terms of clozapine (24), treatment should be personalized by taking into account that its clinical effect is affected by multiple variables, including dose, gender, smoking, age, body weight, caffeine intake, and drug–drug interactions. The clearance of clozapine is principally dependent on the cytochrome P450 (CYP) enzyme 1A2. This enzyme is induced by smoking. For this reason, clozapine levels are generally lower in smokers versus non-smokers (Table 31.10).

Conversely, higher plasma concentrations have been documented in females perhaps due to higher volume of distribution associated with increased body fat in females versus males and in patients between the ages of 45 and 54. Inhibition of CYP1A2 could instead lead to higher clozapine concentrations in case of increased caffeine consumption (CYP1A2 substrate). Monitoring concomitant medication use is needed to protect against potential drug–drug interactions: inhibition of CYP1A2 by drugs such as fluvoxamine, ciprofloxacin and inhibition of CYP3A4 by erythromycin and nefazodone would lead to higher levels. Conversely, induction of CYP3A4 by rifampin or carbamazepine would potentially lead to decreased plasma levels of clozapine and hence loss of efficacy which can have serious consequences since clozapine is used preferentially in individuals with treatment refractory schizophrenia and of the severe psychotic illness. The loss of efficacy can lead the patient to become of danger to self or others (24–26).

TABLE 31.9 Therapeutic drug monitoring with antidepressants and antipsychotics.

Class	Rationale	Concentration:response relationship	Recommendations
Antidepressants Tricyclic antidepressants	Narrow therapeutic index Multiple biological activities Wide individual variability Genetic polymorphism Established therapeutic window for nortriptyline, desipramine, amitriptyline, imipramine	Nortriptyline: 50–150 ng/ml with curvilinear response Desipramine: 100–160 ng/ml Amitriptyline and its metabolite nortriptyline: 75–175 ng/ml Imipramine: 200–300 ng/ml	Useful if: -additional medications are added -clinical status of the patient has changed -compliance issue -change in metabolism and elimination
SSRIs:	Effective plasma concentration is not established; Adverse effects are dose/concentration dependent and can be interpreted as worsening depression; Wide therapeutic index; Low toxicity	Minimum effective dose effect; Flat dose: response curve; Substantial CYP2D6 inhibition by fluoxetine and paroxetine;	No need for routine TDM; Useful for individual dose optimization; Determination of the medication presence
Citalopram		Citalopram: 85 ng/ml on 40 mg/day;	
Escitalopram		Escitalopram: 15–80 ng/ml	
Fluoxetine		Fluoxetine & norfluoxetine: 120–300 ng/ml on 20 mg/day;	
Fluvoxamine		Fluvoxamine: 100 ng/ml on 150 mg/day.	
Paroxetine		Paroxetine: 70–120 ng/ml on 20 mg/day;	
Sertraline		Sertraline: 10–50 ng/ml on 50 mg/day	
Vilazodone* Vortioxetine* SNRISs: Duloxetine* Levomilnacipran*			
Bupropion	Risk of seizures above 450 mg/day Incidence of seizures is dose dependent; Effect due to peak plasma concentration Anorexic patients are at increased risk for seizures	Better response at 10–50 ng/ml of the parent drug; Higher levels of metabolites are associated with the poorer response; Clearance of hydroxybupropion is CYP2D6 dependent Bupropion plus hydroxybupropion 225–1500 ng/ml	Not used routinely due to limited data; Might be useful due to increased risk of seizures and lower efficacy at higher plasma levels; Useful in preventing drug to drug interactions and safety
Venlafaxine Desvenlafaxine	Linear pharmacokinetics Ascending dose-response relationship	Optimal plasma concentration 195–400 ng/ml Venlafaxine plus O-desmethylvanlafaxine 100–400 ng/ml Higher plasma concentration is associated with excessive NE blockade and elevated blood pressure, tachycardia, diaphoresis, tremor	Not used routinely
Duloxetine	Linear pharmacokinetics	At the dose of 40 mg there is 80% 5-HT receptor occupancy 30–120 ng/ml	Not used routinely due to wide safety margin
Nefazodone Trazodone	Nefazodone: Non-linear kinetics hepatotoxicity	No optimal level range 70–1000 ng/ml	Not established
Mirtazapine	Linear pharmacokinetics Multiple metabolites	Broad therapeutic index 30–80 ng/ml	Not established
MAOIs	Antidepressants efficacy correlates with 80% inhibition of platelet MAO	Effect persists even after plasma concentration falls	Inhibition of platelet MAO activity is cumbersome and expensive TDM has limited applications
Antipsychotics Haloperidol	Plasma levels correlate with D2 receptor occupancy and optimal therapeutic response	Optimal range: 4–25 ng/ml Optimal receptor occupancy: 60–80%	Can be used to determine optimal treatment response and in case of suspected DDIs.
Clozapine	Narrow therapeutic index; Multiple mechanisms of action; Multiple metabolites; Large interindividual variability due to extensive metabolism by CYP enzymes; Difficulty detecting early development of toxicity; Delayed onset of action	Threshold therapeutic plasma level: 350–600 ng/ml	Is important in assessing efficacy and safety
Risperidone Paliperidone	Higher levels have been reported to be associated with poorer clinical response and possibility of higher EPS	20–60 ng/ml (37)	Can be considered

(continued)

TABLE 31.9 (continued)

Class	Rationale	Concentration:response relationship	Recommendations
Olanzapine	Dose–response correlation	20–80 ng/ml Level greater than 23.2 ng/ml for olanzapine was associated with improved clinical response (38)	Not established
Asenapine Aripiprazole Iloperidone Quetiapine Ziprasidone Lurasidone*	Dose–response correlation	Asenapine 2–5 ng/ml Aripiprazole 150–500 ng/ml Iloperidone 5–10 ng/ml Quetiapine 100–500 ng/ml Ziprasidone 50–200 ng/ml	Not established.

*No current minimum effective dose plasma levels available.

TABLE 31.10 Monitoring physiological effects of clozapine.

		Clozapine	
Laboratory test	***Baseline***	***Follow-up***	**Drug effect**
Complete blood count (CBC) with differential white blood cell (WBC) and agranulocyte (ANC) count	WBC ≥ 3,500 ANC ≥ 2,000	Initially weekly, After 6 months bi-weekly, After 1 year monthly.	Agranulocytosis ANC < 500/mm^3
	WBC < 3,500 or 50% of the patient's normal count	Repeat counts	Observe for signs of infection
	WBC < 3,500 and/or ANC < 1,500	Twice weekly	Observe for signs of infection
	WBC < 3,000 and/or ANC < 1,500	Daily	Stop treatment
	WBC < 2,000 ANC < 1, 000	Daily until CBC returns to normal	Stop clozapine, initiate reverse isolation, do not rechallenge
Seizures	Obtain history	Seizure risk: 1%–2% <300 mg daily 3%–4% 300–600 mg daily 5% > 600 mg daily	Black box warning regarding dose-dependent risk of seizures.
Liver function tests	X	As clinically indicated	Cholestatic jaundice Increased liver enzymes
EKG	In patients with pre-existing cardiac disease	As clinically indicated	Hypotension Tachycardia Myocarditis
Clozapine level	After treatment initiation or dose adjustment	Therapeutic level: 350 to 600 ng/ml (clozapine and norclozapine)	Clinical effect is influenced by multiple variables: dose, gender, smoking, age, body weight, caffeine intake, and drug–drug interactions.

Interindividual variability in polymorphism of CYP enzymes can play a pivotal role in the drug's efficacy and tolerability. Slow metabolizers are prone to increased risk of side effects and toxicity, whereas rapid metabolizers are more likely to be classified as non-responders due to inadequate plasma levels of the drug.

Polymorphism tests for cytochrome P450 system isoforms are currently used to yield information whether an individual would be an ultra-rapid, extensive (normal), intermediate, or poor metabolizer which in turn would provide crucial information when selecting a psychotropic medication. The frequency of four genotypes varies depending on the ethnicity of the population. Up to 10% of Caucasian populations are poor metabolizers; whereas Chinese population is less than 1%. Asians have an increased risk of being intermediate metabolizers compared to Caucasians. Clinical effects and pharmacokinetic activity of certain medications that are dependent on CYP P450, i.e. risperidone and venlafaxine, will vary significantly amongst individuals of these different populations (25).

A large volume of research on pharmacogenomics has led to changes in the package inserts of a number of drugs that have been prescribed for years. These changes have resulted from data regarding individual differences in drug metabolism and how these differences affect plasma concentration, efficacy and safety.

For example, the package labeling for carbamazepine was changed in 2008 to include a warning regarding the use of the drug in individuals of Asian descent who may be at increased risk of toxic epidermal necrolysis and Stevens-Johnson Syndrome. Even though carbamazepine has been in use since the 1960s, it was only recently identified that *HLA* allele *B*1502* is a marker for these serious dermatological conditions in some groups of Asian individuals (49).

Another example is citalopram, which was approved by the United States Food and Drug Administration (FDA) in 1998 to treat Major Depressive Disorder (MDD). The package labeling for citalopram was changed in 2011 to include a warning regarding the use of higher doses in individuals who are CYP 2C19 poor metabolizers (PM's) because of a greater risk of Torsades de Pointes (50). Several companies have developed assays to genotype individuals in clinical practice because of this warning. Recent FDA CYP2D6 genotype information was the basis for new dose recommendations in pimozide in pediatric and adult patients.

A review of every example of genetic variance and it's effect on drug efficacy or safety is beyond the scope of this chapter. It is important to understand that the age of "one size fits all prescribing" is quickly coming to a close.

Genotyping assays for Cytochrome P450 2C19 and Cytochrome P450 2D6 are currently available for the determination of such polymorphisms. The 2D6 and 2C19 genotyping assays are included in the treatment-resistant depression panel to aid in selecting a proper antidepressant.

31.7.1. Mood Stabilizing Drugs

Returning to the case of Mrs. X, who had been faithfully taking lithium as prescribed initially by the psychiatrist. Her prescription was refilled by the primary care physician with an understanding that she would periodically follow up for TDM of her lithium levels. They had been stable and in 0.8 to 1.0 mEq/L range. She did not experience any adverse effects up until recently when she decided to stop taking all her medications because of difficulty swallowing. She presented for an evaluation to the local emergency room only a week later. At that time, her lithium level was 0.95 mEq/L—a week after the last lithium dose! Lithium has a half-life of approximately 24 hours and under normal conditions will be eliminated after five half lives have elapsed. The ER note indicated severe dehydration and acute renal failure. The recommendation then was made to hospitalize the patient. Unfortunately, lithium was restarted because the previous level (obtained one week after her last dose) was erroneously interpreted as a normal therapeutic level simply because the value was within the therapeutic range. The fact that the patient's level was that high that long after her last dose actually reflected how slow this patient's clearance of lithium was. It is not surprising that the next day the patient presented with worsening symptoms of confusion, ataxia, slurred speech and tremor. Table 31.11 discusses physiologic effects of lithium and corresponding laboratory tests. The decision was made to discontinue lithium and sertraline and treat the underlying delirium. The patient reported significant improvement of symptoms within the next 5 days.

For the purposes of discussion, consider how the laboratory would have played a role in the case of Mrs. X if the decision had been made to switch her from lithium to either valproic acid, carbamazepine, or an atypical antipsychotic after her delirium had cleared.

Tables 31.12 and 31.13 address laboratory testing during the treatment with valproic acid and carbamazepine. Additional laboratory tests could be indicated if the patient is taking oxcarbamazepine, which is associated with hyponatremia. In case of topiramate (27), physicians should be mindful of the possibility of metabolic acidosis and calcium phosphate calculi due to lower urinary citrate excretion and increase in urinary pH.

TABLE 31.11 Monitoring physiological effects of lithium.

		Lithium	
Laboratory test	***Baseline***	***Follow-up***	**Drug effect**
Complete blood count with differential white blood cell count	X	Annually	Benign leucocytosis
Serum electrolyte levels Serum calcium level	X	Every 6 months	Electrolyte balance affects toxicity Hypoparathyroidism
Urinalysis, BUN Serum creatinine level	X X*	Every 6 months and when clinically indicated	Polyuria-polydipsia (nephrogenic diabetes insipidus)
Pregnancy test	X	When clinically indicated	Ebstein's anomaly Tricuspid valve malformation Atrial septal defect
Thyroid function tests	X*	Every 6–12 months	Hypothyroidism
Electrocardiogram	In patients over 40 or with preexisting cardiac disease	Annually	T-wave suppression Arrhythmias Myocarditis Contraindicated in patients with unstable congestive heart failure or sick sinus syndrome
Lithium level	After 5 days of initial dose or dose adjustment; trough level 12 hours after the last dose	Every 6–12 months or as indicated, or 1 week after dose change	Narrow therapeutic index: 0.8–1.2 mEq/L Mild toxicity: 1.5–2.0 mEq/L Moderate toxicity: 2.0–2.5 mEq/L Severe toxicity: >2.5 mEq//L

*Expanded test might be needed if clinically indicated.

TABLE 31.12 Monitoring physiological effects of valproic acid.

Valproic acid			
Laboratory test	***Baseline***	***Follow-up***	**Drug effect**
Complete blood count with differential white blood cell count	X	Annually	Thrombocytopenia
Pregnancy test	X	Document contraceptive method	Neural tube defect (1–2%) Spina bifida (1%)
Liver function tests	X	Every 6–12 months	Hepatotoxicity or liver failure (1:40,000) Elevated LDH/SGOT, SGPT
Serum amylase		When clinically indicated	Life-threatening pancreatitis
Weight Serum lipids Hemoglobin A1C Menstrual cycle	X	Periodic monitoring in female patients	Polycystic ovarian syndrome
Genetic testing	Suspected ornithine transcarbamylase deficiency	Close monitoring	Reye-like syndrome: hyperammonemia, hypoglycemia, encephalopathy.
Valproic acid level	After 3 days of initial dose or dose adjustment; 12 hours after the last dose	Every 6–12 months as indicated	Serum level: 50–125 mcg/ml

TABLE 31.13 Monitoring physiological effects of carbamazepine.

Carbamazepine			
Laboratory test	***Baseline***	***Follow-up***	**Drug effect**
Complete blood count with differential white blood cell count	X	After 1 month; Quarterly for the first year	Leukopenia Bone marrow suppression Agranulocytosis* Thrombocytopenia
Pregnancy test	X	Document contraceptive method since the effectiveness of oral contraceptives can be compromized	Craniofacial defects Spina bifida Developmental delay
Liver function tests	X	q 6–12 months	Hepatotoxicity Transient increase in SGOT, SGPT, alkaline phosphatase Hepatitis Cholestatic jaundice
EKG	In patients with pre-existing cardiac disease	As clinically indicated	A-V conduction defects Arrhythmias Congestive heart failure
Sodium level, Renal function	In older patients; with concomitant use of diuretics or lithium	Close monitoring	Inappropriate antidiuretic hormone syndrome
Carbamazepine level	After 5 days of initial dose or dose adjustment; 12 hours after the last dose	Weekly for the first 2 months, then bi-weekly for another 2 months	Serum level: 8–12 μg/mL**

! Document contraceptive method.
• *Carbamazepine is contraindicated in patients with prior history of bone marrow suppression.
• *Carbamazepine should be discontinued if WBC <3,000/mm^3, absolute neutrophil count <1500 mm^3, platelet count <100,000/mm^3.
• **Carbamazepine induces its metabolism leading to decrease in serum level.

31.7.2. Monitoring the Biological Effects of Drugs

In patients such as Mrs. X with her history of metastatic malignant melanoma and a serious psychiatric illness, the challenges do not stop with discontinuation of medications. The discontinuation raises the possibility that the patient will experience an acute relapse of her psychotic illness with all of its attendant dangers and management problems that a psychotic relapse can pose particularly when the patient is on a general medical or surgical floor. In the case of Mrs. X, lithium toxicity occurred as a result of her starting interferon treatment and developing its adverse effects (nausea, vomiting, decreased appetite), which in turn led to dehydration and subsequent lithium toxicity. As indicated above, the decision was made to discontinue the lithium and also the sertraline as well because of the past episode of mania. The concern here is that antidepressants may

be able to induce rapid cycling particularly in a bipolar patient who is not on a mood stabilizer such as lithium. Dehydration was successfully treated and the symptoms of confusion quickly resolved.

Interindividual variability can make specific patients more or less susceptible to a specific drug, especially if the internal environment (see Table 31.8) changes. Mrs. X was referred for outpatient psychiatric follow-up to assist with future decisions regarding treatment of bipolar disorder concomitantly with the treatment of malignant melanoma. If the decision was made to initiate the treatment with an atypical antipsychotic agent, several laboratory parameters would require periodic monitoring as per recommendation of the American Diabetes Association Consensus Panel (28, 29) (Table 31.14): personal and family medical history at the beginning of antipsychotic treatment, as well as weight or body mass index (BMI), a waist circumference, blood pressure, fasting glucose, and a fasting lipid profile. The panel emphasized serial monitoring of these parameters, focusing particularly on weight or body fat (BMI), at every visit, repeat blood pressure, glucose, and lipids at 3 months or more frequent assessments if there was a greater level of risk. Long-term monitoring of most of these parameters was suggested, as long as antipsychotic treatment continued. There is also an emerging consensus on conducting at least an annual assessment of fasting lipids. These general recommendations are used for atypical antipsychotics as a class without reflecting individual variability of each drug (Table 31.15) to cause metabolic abnormalities and the specific biology of each patient that can make him or her an outlier on the usual dose–response curve for a drug (52–58).

There are numerous studies advocating for and against extensive laboratory testing. The bottom line is: the use of the laboratory should be case and cost-driven (30, 31). Ordering additional laboratory tests simply because a physician feels uncomfortable with an underlying medical condition, would be considered inadequate (30, 32). Tests most frequently ordered by psychiatrists are: (UDS) and complete blood count. The emergency room physicians appear to be in agreement with psychiatrists by frequently ordering the same tests (6, 8, 33). Routine UDS did not appear to affect the disposition from the ER or the subsequent length of stay (34, 35). Nevertheless, it is important to screen for major medical disorders since the diagnosis can frequently be missed in patients admitted to psychiatric hospitals (36). Mrs. X might never develop another manic episode and remain symptom free or might be forced to seek an expert opinion from a skillful clinician who would be able to sort through the case and put the pieces of the puzzle together by realizing that medicine remains an art and laboratory testing includes many dependent variables best interpreted from the individual patient's perspective by utilizing available general knowledge fund. Laboratory use in psychiatry serves an auxiliary role in helping physicians identify major differential diagnosis points, guide treatment and anticipate the outcome. Even though the results of laboratory tests are reported in relation to available normal range, clinical significance should be determined in each individual case. Skillful use and interpretation of laboratory tests should aid in identification of an underlying condition and lead to a better understanding of the disease process.

TABLE 31.14 Monitoring recommendations for patients treated with antipsychotic medications.

	Start	4 Weeks	8 Weeks	12 Weeks	6 Months	12 Months	5 Years
Individual/family history	X					X	
Weight (BMI)	X	X	X	X	X		X*
Waist circumference	X					X	
Pulse and blood pressure	X			X		X	
HgA1C	X			X		X	
Fasting lipid profile	X			X			X
CBC	X						
ECG	X,	ziprasidone, clozapine, and medications affecting QTc interval					
Pregnancy test	X						
Suicidality	X,	then periodically					
LFTs	X,	then periodically, if significant hepatic disease					
Slit lamp exam	X				X		
For patients treated on quetiapine							
Renal panel	X,	risperidone, paliperidone, lurasidone					
Risk for orthostatic hypotension at baseline for all							

Clinical status may warrant more frequent assessments.

TABLE 31.15 Risk of weight gain, diabetes, and dyslipidemia for selected antipsychotic drugs.

Drug	Weight gain risk	Relative diabetes risk	Dyslipidemia	Reference
Clozapine	High	High	High	(54, 55, 58)
Olanzapine	High	High	High	(54, 56, 58)
Risperidone	Moderate	Moderate	Moderate	(54, 56, 58)
Quetiapine	Moderate	Moderate	Moderate	(54, 56, 58)
Aripiprazole	Low	Low	Low	(54, 57, 58)
Ziprasidone	Low	Low	Low	(54, 56, 58)

31.8. Biomarkers in Clinical Practice

It is not surprising that in psychiatry the clinical interview is the "gold standard" for diagnosing mental illness. The diagnosis of the major classes of psychiatric illness have not yet been correlated with clinically usable biomarkers, which do not play a large role in the diagnosis or validation of mental illness at this time.

An example of a biomarker that has been explored in psychiatry is cortisol, which was evaluated as a potential biomarker for depression (39). This work led to the use of the dexamethasone suppression test (DST) as a diagnostic tool for major depression (40). Unfortunately, the DST lacked the sensitivity and specificity to be a meaningful diagnostic tool for major depression, although it has utility in other areas of medicine.

While their use in clinical psychiatry is currently limited, biomarkers are serving as critical endpoints in clinical psychiatric research. The use of biomarkers in clinical trials has dramatically improved the ability to assess the efficacy and safety of investigational new drugs. In such trials, biomarkers may be used as a surrogate marker for illness severity or as a measure of whether the investigational drug has reached its target at an appropriate rate and concentration.

Most biomarkers are developed via pathway analysis, proteomics, and DNA expression profiles. In order to be validated, biomarkers must be compared to established clinical endpoints (i.e., antipsychotic efficacy).

Positron Emission Tomography (PET), which involves the use of radio-labeled isotopes, is an example of a technique capable of measuring brain-specific biomarkers used in clinical trials to measure drug binding to specific target receptors. PET may also be used to evaluate interactions with specific neurotransmitter systems (41). Such work can establish whether a specific drug reaches the desired target in the brain and what concentration is needed to modulate the target to an appropriate degree, particularly when such targets are necessary to produce the drug's effect. This type of biomarker work led to the recognition that 65% to 85% occupancy of the D2 receptors was necessary for antipsychotic effect (42).

Another example involves the use of saccadic eye movements and prolactin response in the development of antipsychotic drugs (43). Each have been correlated with maximum tolerated dose as well as the development of adverse events.

In the area of antidepressant drugs, the Biomarkers for the Rapid Identification of Treatment Effectiveness in Major Depression (BRITE-MD) study showed that pre-frontal lobe activity at one week of treatment with escitalopram correlated with efficacy seven weeks later (44). Additional biomarkers in the development of antidepressant drugs include the effect of the drug on REM sleep (45), changes in EEG (46), and the use of PET to determine percent occupancy of the serotonin transporter (47).

Advances in Alzheimer's disease research at the 65th Annual Meeting of the American Academy of Neurology highlighted amyloid and tau protein levels in the brain and CSF as well as introduction of possible new biomarker, PKR, a kinase indirectly involved in phosphorylation of tau (48). The development of biomarkers for specific illnesses will not only improve the drug development process, but could change psychiatric diagnosis and treatment dramatically from the approaches used today.

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Epidemiology of Psychiatric Illness

Celia F. Hybels, Ph.D. and Dan G. Blazer, M.D., Ph.D.

Abstract The science of epidemiology has much to offer in assisting clinical investigators and practicing psychiatrists to place the work on inpatient units and outpatient clinics into context. Epidemiologists first emphasize the importance of case identification and finding (who is a case of, for example, major depression and who is not). Once a method of case identification is established, the frequency and distribution of cases in varying populations (such as the community or general medicine clinic) can be established. New cases can be enumerated from a population at risk over time (for example, estimating the one-year incidence of major depression in a community). Epidemiology has been most instrumental through informing our current nomenclature as to the nature and extent of psychiatric disorders which are comorbid. Mental health service use, especially in community-based populations, is another focus of psychiatric epidemiology. Finally, psychiatric epidemiology assists investigators and clinicians to identify risk factors for psychiatric disorders, ranging from demographic factors to biological risks. The preliminary explorations into risk provide the basis for more extensive studies of etiology.

Keywords Epidemiology · Prevalence studies · Incidence studies · Etiology · Comorbidity

In their classic textbook, MacMahon and Pugh define epidemiology as the study of the distribution and determination of disease frequency in humans (1). In this context, the science of epidemiology has much to offer the field of psychiatry. Psychiatric disorders vary in their distribution across age groups and sex. For example, major depression is more frequent among women and young adults than among men and older adults. Within disorders, the symptoms endorsed may differ across various demographic subgroups. For example, depressed older adults may be less likely to endorse feelings of sadness (2). In epidemiology, the focus is the distribution of disease in a specified population, with distribution defined as both the proportion of people in a population with the disease at a given point in time and the proportion of people who are disease-free who develop the disease in an identified time period. In psychiatric epidemiology, the etiology of disorders is studied through the patterns of risk factors associated with the disorders in specified populations. Rothman and Greenland concluded that the goal of most epidemiologic research is to elaborate on causes that can explain the pattern of disease occurrence (3).

This chapter introduces key terms that are central to understanding the epidemiology of psychiatric illness and describes some methodologic issues in psychiatric epidemiology. We then provide information on the frequency and distribution of psychiatric disorders and address their etiologies through a discussion of various risk factors. The data we present derive primarily from community studies of adult populations (4–10).

C.F. Hybels, Ph.D. (✉)
Associate Professor, Department of Psychiatry and Behavioral Sciences,
Duke University Medical Center, Durham, NC, USA
e-mail: celia.hybels@duke.edu

D.G. Blazer, M.D., Ph.D.
J.P. Gibbons Professor of Psychiatry, Department of Psychiatry and Behavioral Sciences,
Duke University Medical Center, Durham, NC, USA
e-mail: dan.g.blazer@dm.duke.edu

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32.1. Applications of Epidemiology

Epidemiologic methods have historically been applied in four general ways to the study of psychiatric illness:

- Descriptive epidemiology. Clues to the etiology of psychiatric illness have been sought through the study of the association of cases with various characteristics (e.g., age, sex, social class). Descriptive epidemiology serves to generate hypotheses.
- Analytic epidemiology. Once etiologic hypotheses have been identified through descriptive studies, they can be tested using a variety of analytic strategies comparing the relative frequency with which persons with a given risk factor (e.g., a positive family history) or set of risk factors for a specific disorder develop that disorder during a period of time as compared with people without such a risk factor. For disorders that are rare, epidemiologists may compare the probability of a particular exposure among those with the disease to the probability of exposure in a control group without the disease.
- Experimental epidemiology. Once a suspected etiologic risk factor has been identified, experiments may be carried out in which the investigator artificially manipulates this risk factor while holding all other variables constant. The use of this experimental approach within psychiatry has, for the most part, been limited to clinical therapeutic trials. However, psychiatric epidemiologists have capitalized on naturally occurring quasi-experimental situations, such as natural disasters, having a heart attack, or being informed of a cancer diagnosis, to study the effects of a specific risk factor on the subsequent development of psychiatric illness or condition.
- Program planning and evaluation. Results of descriptive studies have been widely used to estimate the need for mental health services in defined populations (11), to identify ethnic disparities in unmet need (12), and to identify predictors of the type of help used (13). Studies such as these have been used to develop more effective and efficient approaches to the delivery of mental health services.

32.2. Key Terms and Methodologic Issues in Psychiatric Epidemiology

A critical understanding of the findings of epidemiologic studies of psychiatric illness requires knowledge of key terms used and an appreciation of the methodologic problems inherent in the epidemiologic method.

32.2.1. Incidence and Prevalence

Incidence is defined as the number of new cases per unit time divided by the average population at risk during the time period. *Prevalence* is the proportion of cases present in the population. *Point prevalence* is defined as the number of existing cases at one point in time divided by the average population at risk at that point in time. *Period prevalence* is defined as the number of existing cases during a period of time divided by the average population at risk during that time period.

These primary measurements of epidemiology (incidence and prevalence) require a numerator (cases), a denominator (population at risk), and a time frame.

32.2.1.1. Numerator Data

The accurate enumeration of cases requires a specific definition of a case and the detection of all cases in the study population. Most studies have used either treatment source information or community surveys to estimate the number of cases present in the population. Both sources have potential drawbacks. For example, the use of mental health services is known to be influenced by a variety of demographic variables (including age, sex, race, and especially the distance one lives from the treatment facility) as well as characteristics of the facility itself (e.g., number of beds available, accessibility, reputation in the community, admission policies) and public policy (e.g., legislation discouraging the admission of older adults).

Community survey data have advantages and disadvantages that mirror those of treatment source data. Surveys are generally much more expensive and time consuming to carry out. Therefore, most surveys cannot assess the total population to ascertain the total number of cases and must rely on a sampling of the population. In order to ensure that the findings of the survey are representative of the population surveyed, probability sampling techniques must be used in which the investigator can specify the probability that each person in the population will be included in the survey sample. Community surveys with complex probability sampling designs often rely on cluster sampling for efficiency, resulting in a potential bias in that persons who reside near each other in clusters may be more similar to each other than to those who live in different areas. Epidemiologists sometimes use special analytic software to adjust for these design effects. Community surveys also require a method to determine the presence of a psychiatric disorder. Because diagnosis of every respondent by a clinician is prohibitively expensive, most

surveys rely on either questionnaires completed by respondents or structured interviews by nonclinician interviewers. In either case, the survey instruments must meet tests of reliability (lack of systematic error) (3) and validity (the capacity to give the same result in repeated measurements) (3) to ensure that those identified as cases would be diagnosed as such if a clinician examined them. The major advantage of the community survey is its ability to ascertain in a relatively unbiased way the proportion of people in the study population with definable disorders.

32.2.1.2. Denominator Data

An estimate of the population at risk is usually obtained from census data. Thus, the main problems involve the extent to which the true population size might be underestimated by the census and the proximity in time between the collection of numerator and denominator data. These biases are more pronounced when treatment source data are used to estimate the number of cases, since surveys will ascertain both numerator and denominator information directly. However, with survey data, the response rate becomes crucial, because people who refuse to participate in surveys or who cannot be located are likely to have a higher rate of psychiatric disorder than those who do participate.

32.2.1.3. Time Perspective

In general, for episodic conditions, such as episodes of major depression, prevalence is the product of incidence and duration. For etiologic investigations, incidence estimates are more useful than prevalence estimates, because factors that affect the duration of the condition but that are unrelated to its cause will be associated with prevalence, whereas only factors causative of the illness will be associated with incidence. However, for rarely occurring disorders, in which the exact time of onset of the illness cannot be accurately determined (characteristic of many psychiatric disorders), incidence data may be either impossible or inordinately expensive to collect. To compensate partially for this situation, psychiatric epidemiologic studies have used the concept of lifetime prevalence (i.e., the probability of a respondent ever having experienced a specific condition up to the date of assessment). This risk will be influenced by the age of the population (the proportion of people who have had the opportunity to develop the disease), mortality from the disorder, and the inability to recall a disorder that happened years ago (14).

32.2.2. Definition of a Case

The most crucial variable in any epidemiologic study, and one that may account for variation in study findings, is case definition.

Historically, psychiatric epidemiologic studies have used different concepts of case definition and, consequently, have obtained different rates of illness occurrence. In studies carried out in Europe and in the USA before World War II, mental illness was considered to not be a unitary concept, but one with discrete, categorically distinct disorders with different etiologies and differing treatments. Cases were defined according to diagnostic criteria current at the time, and rates of illness were calculated separately for these disorders (15).

In contrast, after World War II, in the predominant psychiatric epidemiologic studies in the USA, mental disorder was seen as unitary and on a continuum, rather than as a set of diagnostically distinct conditions. In addition, health was defined as the absence of symptoms or functional impairment and was categorized according to intensity or severity of symptomatology or impairment, despite the fact that most of the population is not totally asymptomatic or totally functional at any point in time (16). Thus, these studies reported high rates of mental impairment (e.g., the Midtown Manhattan Study found only 19% of the population to be free of significant symptoms, whereas 23% were significantly impaired) (17). However, these studies substantially advanced survey methodology in the areas of sampling, instrument development, and statistical analysis, but could not generate rates of specific psychiatric disorders.

As noted by Weissman and Klerman (16), beginning in the 1960s, several events occurred that significantly influenced psychiatric epidemiology. Research strategies in genetic psychiatry—chiefly twin studies, family studies, and adoption and cross-fostering techniques, as well as the development of sophisticated methods of statistical analysis—strengthened the evidence for the existence of discrete psychiatric disorders with different patterns of heritability. In addition, advances in the biologic treatment of psychiatric disorders, including the use of electroconvulsive therapies, as well as the development of psychopharmacologic agents with specific clinical effectiveness for specific disorders, supported the concept of specific psychiatric disorders as opposed to the unitary concept of mental illness.

Both these sets of developments highlighted the need for valid and reliable diagnostic criteria. The epidemiologic observation of markedly different treated prevalence rates for schizophrenia and mood disorders between the USA (where schizophrenia was about one third more prevalent) and the UK (where the prevalence of mood disorders was several times greater) led to a series of studies (18, 19) that demonstrated that these differences were largely attributable to the different diagnostic practices of British

and American psychiatrists rather than to differences in the actual prevalence of the two disorders. When structured interviewing techniques and specified diagnostic criteria were used, good reliability among clinicians and researchers could be obtained. In the USA, the first published, specified criteria for a subset of mental disorders were the Feighner criteria (20). Subsequently, a set of Research Diagnostic Criteria (RDC) was developed (21). These developments provided impetus for a third revision of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-III) (22) of the American Psychiatric Association which became the official US psychiatric nosology in 1980, the most recent revision of which (DSM-5) was published in 2013 (23).

The impact of these diagnostic developments on psychiatric epidemiology in the USA has been far reaching. Most US epidemiologic studies from World War II to the mid-1970s defined illness in terms of symptom frequency or intensity or functional impairment. A case was, therefore, not defined by specific symptoms, but rather by an assessment of the severity and impairment secondary to psychiatric symptoms. Although many, if not most, psychiatrically ill individuals will score highly (as "cases") on such instruments, many persons with no diagnosable psychiatric disorder will also score in the "case" range. Dohrenwend et al. (24) have described these clusters of symptoms that cut across diagnostic criteria and, therefore, do not define cases as indicators of nonspecific psychological distress or demoralization (25). In addition, these measures do not permit the identification of people with diagnosable conditions (true positive) from those without diagnoses (false positive), that is, discrete cases of mental illness. Thus, these nonspecific measures do not permit the calculation of incidence and prevalence rates by specific diagnoses, a prerequisite for the development or testing of specific etiologic hypotheses.

The first study in the USA that applied these specified diagnostic criteria to a community sample was a pilot study of 500 people carried out by Weissman and colleagues (26) using the RDC criteria. After the conclusions of this study, the Division of Biometry and Epidemiology of the National Institute of Mental Health initiated the development of a new instrument, the Diagnostic Interview Schedule (DIS), which could be administered by lay interviewers, thus permitting its use in large-scale studies (27). The DIS was constructed to elicit diagnoses according to Feighner, RDC, and DSM-III criteria for a subset of adult DSM-III diagnoses selected on the basis of prevalence, clinical significance, and scientific validity based on treatment response, family studies, and follow-up studies (27). This instrument was then used in a series of community surveys—the Epidemiologic Catchment Area (ECA) Study—conducted in five locations (New Haven, Baltimore, St. Louis, Los Angeles, and North Carolina), each site including approximately 3,000 community respondents.

The ECA was a landmark study for psychiatric epidemiology and was soon followed by other studies of the prevalence of psychiatric disorders in a number of geographic areas using DSM-III. In the USA, the National Comorbidity Survey (NCS) was conducted in the 1990s, the first study of the prevalence of psychiatric disorders in community-dwelling adults ages 15–54 using a nationally representative sample (5). The NCS used a semi-structured interview, the Composite International Diagnostic Interview (CIDI) (28). Similar to the DIS, the CIDI could be administered by lay interviewers, and the responses could be used to generate DSM-III-R diagnoses. A version of the CIDI that can generate DSM-IV diagnoses was used in the WHO World Mental Health Surveys (MHS) (7). Similarly, the National Epidemiologic Survey of Alcohol and Related Conditions (NESARC) used the Alcohol Use Disorder and Associated Disabilities Interview Schedule DSM-IV (AUDADIS-IV) (29) to match disorders to DSM-IV criteria.

It is important to note psychiatric disorders are currently defined in the nomenclature by their symptom presentation, but current research is exploring the role of both genetic factors and biological risk factors such as the structure of the brain, neural circuitry, and the volume of small-vessel disease evident through neuroimaging as they relate to specific diagnoses.

32.2.3. Reliability and Validity of Diagnostic Instruments

Even given the availability of valid diagnostic criteria such as those provided by DSM-5, the instruments used to gather these data must meet tests of reliability and validity in their construction and administration. If constructed and administered properly, it would be expected that scores on the instrument would always reflect true differences in the characteristic being measured (e.g., a person reporting symptoms of schizophrenia should "truly" have a schizophrenic diagnosis). However, a number of other factors may cause spurious variations in scores. For example, differences in transient symptoms such as fatigue, situational factors such as stress, ambiguous questions in the interview, or a language barrier may produce invalid data. In addition, the administration of the instrument may be subject to error introduced by some factor that systematically affects the characteristic being measured or the interview process (e.g., sex or race of interviewer and respondent). To minimize these spurious sources of variation, instruments must meet tests of reliability and validity.

Reliability is the amount of variation in scores among individuals that is due to inconsistencies in measurement (30). In epidemiologic surveys, reliability is generally tested in terms of:

- Test-retest reliability: The same test is administered at different times and the results are correlated. However, if the two tests are repeated too closely in time, there may be a spurious inflation of reliability owing to memory of the earlier test, whereas if clinical change occurs between administrations, the reliability will be artificially lowered.

- Interrater reliability: The observation of the same interview by two or more raters, each of whom independently scores the results.

Validity is the extent to which differences in scores reflect true differences in the characteristic that the test measures and the degree to which the instrument measures what is intended. Measures of validity include:

- Predictive validity: The ability to predict a future event by knowledge of the test score (e.g., a diagnosis of depression should predict responsiveness to antidepressant treatment).
- Concurrent validity: The ability to predict the presence or absence of an event when compared with a known criterion (e.g., a diagnosis of depression should correlate with biologic measures indicative of depression).
- Content validity: A measure of the pertinence of the instrument to the characteristic tested and the extent to which all aspects of the characteristic are tested (e.g. a depression scale should contain symptoms characteristic of depression).
- Construct validity: The relation of the score to other related aspects of the condition (e.g. a depression scale should show higher scores in depressed patients than in nondepressed individuals).

Overall, reliability does not guarantee validity, but validity cannot be established without reliability.

32.2.4. Sensitivity and Specificity

In evaluating the usefulness of an instrument designed to provide diagnostic information, results are compared with a standard criterion to determine the instrument's sensitivity (i.e., the extent to which people who truly have a characteristic are classified as such) and specificity (i.e., the extent to which people who do not have the characteristic are so classified) (1). In the case of psychiatric diagnoses, since no "objective" diagnostic tests are available, the instrument results are usually compared with diagnoses made by experienced clinicians.

An instrument's *sensitivity* is the proportion of true-positive results identified among those declared positive, while the *specificity* is the proportion of true-negative results identified among those classified as negative by the instrument. For an instrument to be useful in epidemiologic investigations, it should demonstrate high sensitivity and at least moderately high specificity, because the more crucial characteristic is its ability to detect cases, especially in view of the relatively low prevalence of most specific psychiatric disorders. In this regard, the DIS was one of the first diagnostic instruments used in psychiatric epidemiology to have been exposed to rigorous tests of sensitivity and specificity before its field application (27). Most earlier studies demonstrated evidence of satisfactory reliability with little attention to validity issues.

32.3. Descriptive Epidemiology: Prevalence Studies

Before the publication of DSM-III (22), which defined disorders more by their symptoms than their etiology, community studies of the prevalence of psychiatric disorders were less common because of the necessity to engage clinicians in the diagnoses. Prevalence estimates were generally based on the proportion of psychiatric illness observed in clinical samples.

The ECA survey (31) was the first large-scale study of the prevalence and incidence of psychiatric disorders in community and institutional populations. The target population was all adults aged 18 years or over living in a designated mental health catchment area, and the sampling frame included residents of both households and institutions. As previously mentioned, the ECA used the DIS (27) to obtain information on a series of symptoms, which could then be mapped to DSM-III, and used to generate diagnoses. Results of the ECA surveys have been documented in detail (14). Prevalence estimates for community residents are reported in Table 32.1. Participants in the ECA were reinterviewed using the DIS 12 months after the baseline interview.

Other large-scale epidemiologic studies using the DIS followed the ECA. One example is a population-based study of 3,258 adults 18 or older in Edmonton, Alberta, with an additional sample of 358 elderly living at home. Similar to the ECA, an institutional sample was included. Prevalence estimates were similar to those obtained in the New Haven ECA data, with the exception of a higher prevalence of cognitive impairment in New Haven (32).

In the NCS (5), a total of 8,098 adults aged 15–54 years selected from a stratified, multi-staged probability sample were interviewed. Psychiatric diagnoses were based on DSM-III-R (33) criteria, which were in place at the time of the survey. Prevalence estimates obtained from the NCS are provided in Table 32.1.

Other epidemiologic studies using the CIDI followed, an example of which is the Netherlands Mental Health Survey and Incidence Study (NEMESIS) conducted in 1996 (6). A total of 7,076 noninstitutionalized Dutch adults ages 18–64 years were interviewed using the CIDI. The NEMESIS was a longitudinal study, with follow-up assessments at 12 and 36 months after the baseline assessment. Prevalence estimates of psychiatric diagnoses based on DSM-III-R criteria are provided in Table 32.1.

The WHO World MHS were conducted in 14 countries (7), and diagnoses were based on DSM-IV criteria (34). In the USA, the survey was called the NCS Replication (NCS-R) (35). A total of 9,282 adults 18 years or older were interviewed, selected from a representative sample, and prevalence estimates are provided in Table 32.1. We have also included estimates from three other

TABLE 32.1. Prevalence of psychiatric disorders in selected community-based studies.

	ECA		NCS		NEMESIS			NCS-R		M-NCS	ESEMeD		C-MHS	NESARC	NLAAS
Selected disorders	LT	1 Mo	LT	12 Mo	LT	12 Mo	1 Mo	LT	12 Mo	12 Mo	LT	12 Mo	12 Mo	LT	12 Mo
Any psychiatric disorder assessed	32.2	15.4	48.0	29.5	41.2	23.2	16.5	46.4	26.2	12.1	25.0	9.6	7.0		13.6
Any substance use disorder	16.4	3.8	26.6	11.3	18.7	8.9	5.8	14.6	3.8	2.5			1.6		1.3
Alcohol abuse/dependence	13.3	2.8								2.2	5.2	1.0	1.6		
Drug abuse/dependence	5.9	1.3								0.5			0.1	10.3	
Schizophrenia	1.3	0.6			0.4	0.2	0.2								
Any affective/mood disorder	8.3	5.1	19.3	11.3	19.0	7.6	3.9	20.8	9.5	4.8	14.0	4.2	2.2	19.5	5.0
Mania/bipolar	0.8	0.4	1.6	1.3	1.8	1.1	0.6	3.9	2.6	1.1			0.1	3.3	
Major depression	5.8	2.2	17.1	10.3	15.4	5.8	2.7	16.6	6.7	3.7	12.8	3.9	2.0	16.5	4.6
Dysthymia	3.3	3.3	6.4	2.5	6.3	2.3	1.6	2.5	1.5	0.4	4.1	1.1	0.1	4.3	1.6
Any anxiety disorder	14.6	7.3	24.9	17.2	19.3	12.4	9.7	28.8	18.1	6.6	13.6	6.4	2.7	16.2	10.0
Phobia	12.5	6.2													
Panic	1.6	0.5	3.5	2.3	3.8	2.2	1.5	4.7	2.7	0.6	2.1	0.8	0.2		1.5
Panic with agoraphobia														1.1	
Panic without agoraphobia														4.0	
Agoraphobia without panic			5.3	2.8	3.4	1.6	1.0	1.4	0.8	0.7	0.9	0.4	0.0		
Agoraphobia with or without panic															0.3
Social phobia			13.3	7.9	7.8	4.8	3.7	12.1	6.8	1.7	2.4	1.2	0.2	5.0	3.0
Specific/simple phobia			11.3	8.8	10.1	7.1	5.5	12.5	8.7	4.0	7.7	3.5	1.9	9.4	
Generalized anxiety			5.1	3.1	2.3	1.2	0.8	5.7	3.1	0.4	2.8	1.0	0.8	4.1	1.4
Post-traumatic stress disorder								6.8	3.5	0.6	1.9	0.9	0.2		1.3
Obsessive-compulsive disorder	2.5	1.3			0.9	0.5	0.3	1.6	1.0						
Severe cognitive impairment	1.3	1.3													

LT = lifetime. ECA = Epidemiologic Catchment Area surveys; 5 US sites; 18,571 adults 18+; DIS (DSM-III) (4). NCS = National Comorbidity Survey, representative sample in the USA; adults 15–54; CIDI (DSM-III-R) (5). NEMESIS = Netherlands Mental Health Survey and Incidence Study; representative sample in the Netherlands; 7,076 adults 18–64; CIDI (DSM-III-R) (6, 42). NCS-R = National Comorbidity Survey Replication (part of WHO World Mental Health Survey); representative US sample; 9,282 adults 18+; CIDI (DSM-IV) (35, 39). M-NCS = Mexico National Comorbidity Survey (part of WHO World Mental Health Survey); representative sample; adults 18–65; CIDI (DSM-IV) (36). ESEMeD = European Study of the Epidemiology of Mental Disorders (part of WHO World Mental Health Survey); 21,425 adults 18+; CIDI (DSM-IV) (37). C-MHS = China World Mental Health Survey (part of WHO World Mental Health Survey); 5,201 adults 18–70 in Beijing and Shanghai; CIDI (DSM-IV) (40). NESARC = National Epidemiologic Survey on Alcohol and Related Conditions; representative US sample; adults 18+; AUDADIS-IV (DSM-IV) (8). NLAAS = National Latino and Asian American Study; representative US sample; adults 18+; CIDI (DSM-IV) (99).

MHS sites: Mexico, Europe, and China. In the Mexican NCS (M-NCS), a representative sample of 5,826 adults aged 18–65 years participated (36). In the European Study of the Epidemiology of Mental Disorders (ESEMeD), a representative sample of 21,425 adults 18 years or older was selected from Belgium, France, Germany, Italy, the Netherlands, and Spain (37). The World MHS was also conducted in two areas of China: Beijing (B-WMH) and Shanghai (S-WMH). A total of 5,201 adults aged 18 years or older were interviewed from a representative probability sample of those two areas. Prevalence estimates are provided in Table 32.1.

The NIMH Collaborative Psychiatric Epidemiology Surveys (CPES) joined three nationally representative surveys—the NCS-R, the National Survey of American Life (NSAL) of Africans and Caribbean blacks, and the National Latino and Asian American Study (NLAAS) with a core interview structure—allowing as NIMH describes a twenty first century benchmark of the prevalence and correlates of mental disorders in the US population (38). The NESARC baseline survey was conducted in the USA in 2001–2002, and participants were reinterviewed in 2004–2005 (8). A total of 43,093 adults aged 18 years or older were selected through a representative sample of the US adult population. Prevalence estimates of selected disorders based on the AUDADIS-IV are provided in Table 32.1.

Table 32.1 presents the prevalence estimates from some of the large-scale psychiatric epidemiologic studies discussed above. Overall, the prevalence estimates are fairly consistent, but differences are also noted. In comparing the prevalence reported from various studies, it is important to note the nomenclature in effect at the time the survey was completed. For example, the criteria for generalized anxiety were changed between DSM-III and DSM-III-R. Second, there is variation associated with the period assessed. For example, lifetime prevalence is higher than 12-month prevalence. In addition, different diagnostic instruments may produce different estimates. Even when the sample, instrumentation, and data collection design is common to multiple sites, such as in the WHO World MHS, the prevalence estimates may differ across cultures. Finally, it is important to note the age range of the sample when making comparisons, especially when comparing the prevalence of disorders that vary across age groups.

These studies indicate that, overall, the lifetime prevalence of any psychiatric disorder is very high. In the NCS-R, which includes adults across all age groups, the lifetime prevalence of any DSM-IV disorder was 46.4% (39). The lifetime prevalence of any anxiety disorder (28.8%) was higher than the lifetime prevalence of any mood disorder (20.8%) or substance use disorder (14.6%). Lifetime prevalence estimates are potentially affected by recall bias and selective survival.

In the NCS-R, the most prevalent disorders based on 12-month estimates were specific phobia (8.7%), social phobia (6.8%), and major depressive disorder (6.7%) (35). A similar pattern was observed in the other MHS components (36, 37, 40).

32.3.1. Distribution of Psychiatric Disorders Across Demographic Subgroups in Prevalence Studies

One of the goals of epidemiology is to examine the distribution of disease in the population. Data from community-based psychiatric epidemiology studies drawn from representative samples are an excellent source of information to identify the prevalence of disorders across various demographic subgroups.

32.3.1.1. Age

The one-month prevalence of any psychiatric disorder from the ECA study was 16.9% among those aged 18–24 years, 17.3% among those aged 25–44 years, 13.3% among those aged 45–64 years, and 12.3% among those aged 65 years or older (4). Among those aged 18–24 years, the most prevalent disorders were phobic disorder (6.4%) and alcohol (4.1%) and drug (3.5%) use disorders. Among those aged 25–44 years, the most prevalent disorders were phobic disorders (6.9%), dysthymia (4.0%), alcohol use disorders (3.6%), and major depression (3.0%). Among those aged 45–64 years, the most prevalent disorders were phobic disorder (6.0%) and dysthymia (3.8%). Among those aged 65 years or older, cognitive impairment (4.9%) and phobic disorder (4.8%) were most prevalent.

In the NCS, the odds of having any disorder in the past 12 months decreased with age. Compared to persons aged 45–54 years (the oldest age group in this sample), the odds of any disorder were increased for those aged 35–44 years (OR = 1.24), those aged 25–34 years (OR = 1.51), and for those aged 15–24 years (OR = 2.06) (5). That is, compared to those aged 45–54 years, the probability of having a psychiatric disorder was 1.24 times higher among those aged 35–44 years, 1.51 times higher among those aged 25–34 years, and 2.06 times higher among those aged 15–24 years. The 12-month prevalence of any disorder was 27.6% among those aged 18–44 years, 22.4% among those aged 45–64 years, and 8.5% among those aged 65 years and older (41). A similar pattern was observed in the NEMESIS, where the prevalence of one or more disorders in the past 12 months was 14.9% among those aged 55–64 years and 33.8% among those aged 18–24 years old (42). Significant differences by age were also reported in the ESEMeD project, where the 12-month prevalence of any mental disorder was 13.7% among those aged 18–24 years and 5.8% among those aged 65 years or older (37). In both the M-NCS and the C-MHS, the 12-month prevalence of a disorder classified as serious (e.g., associated with suicide attempt or severe role impairment) was not significantly different by age group, but the prevalence of any disorder was highest among those aged 18–34 years old (7, 36, 40).

TABLE 32.2. Lifetime prevalence of selected mental disorders by sex across all age groups.

DSM-IV disorder	Men (%)	Women (%)
Anxiety disorders		
Panic disorder	3.1	6.2
Agoraphobia without panic	1.1	1.6
Specific phobia	8.9	15.8
Social phobia	11.1	13.0
Generalized anxiety disorder	4.2	7.1
Posttraumatic stress disorder	3.6	9.7
Any anxiety disorder	22.4	32.4
Mood disorders		
Major depressive	12.9	20.0
Any mood disorder	14.8	22.9
Substance abuse disorders		
Alcohol abuse	11.7	4.4
Drug abuse	11.5	4.8
Any substance use disorder	17.9	7.3
Any schizophrenic disorder	1.2	1.7

Data for anxiety, mood, and substance use disorders obtained from the National Comorbidity Survey Replication. Reprinted from (41) Copyright (2009) with permission from Elsevier.
Data for any schizophrenic disorder obtained from the ECA data using DSM-III (14).

32.3.1.2. Sex

Across most disorders, the current prevalence is higher in women than men. In the ECA, the 1-month prevalence of any disorder was 16.6% for women and 14.0% for men (4). Among women, the most prevalent disorders were phobic disorder (8.4%), dysthymia (4.2%), and major depression (2.9%), whereas among men, the most prevalent disorders were alcohol use disorders (5.0%) and phobic disorders (3.8%). In the NCS, women were 1.76 times more likely to have a mood disorder, 2.19 times more likely to have an anxiety disorder, and less likely to have any substance use disorder (OR = 0.37) in the past 12 months compared to males (5). A similar pattern was observed in the NEMESIS, where the 12-month prevalence of any disorder did not significantly vary by sex, but women were more likely to report mood and anxiety disorders and less likely to report substance use disorders (42). In the C-MHS, women were less likely to have one or more disorders in the past 12 months, but 3.0 times more likely to have a severe disorder (40). Differences in the 12-month prevalence of severe disorders in the M-NCS were not significant, but women were more likely to have a mood or anxiety disorder and less likely than men to have a substance use disorder (36). Women are more likely than men to have a lifetime anxiety or mood disorder, while men are more likely to have a lifetime substance use disorder. The lifetime prevalence of selected mental disorders by sex across all age groups from the NCS-R is shown in Table 32.2.

32.3.1.3. Race/Ethnicity

The ECA data (14) showed an increased prevalence of total mental disorders among blacks (38% lifetime, 26% 1 year), which was most prominent in the population older than 45 years of age. However, when controlled for age, gender, marital status, and socioeconomic status, there were virtually no significant differences in ethnicity by specific diagnostic categories.

By contrast, in the NCS, blacks were less likely than whites to have any 12-month psychiatric disorder (OR = 0.70). Hispanics were more likely than whites to have a mood disorder within the past 12 months (OR = 1.38), and blacks were less likely to meet criteria for a substance use disorder than whites (OR = 0.47). Hispanics were 1.86 times more likely to have 3 or more comorbid disorders in the past 12 months compared to whites (5).

Recent studies have included non-English-speaking participants in the sample. In the NLAAS, the lifetime prevalence of any psychiatric disorder was 28% among men and 30% among women, whereas the 12-month estimates were 13% and 17%. The prevalence was higher among those in the Puerto Rican ethnic group compared to Caribbean, Mexican, and other Latinos (9). In the NESARC, the prevalence of any psychiatric disorder was significantly lower among Asian Americans/Pacific Islanders compared to non-Hispanic whites (43).

32.4. Descriptive Epidemiology: Incidence Studies

Psychiatric disorders are often chronic, and cases can be readily identified through prevalence studies. Because of the relatively infrequent occurrence of specific psychiatric disorders, their tendency to recurrence, and the difficulty of estimating the onset of the illness, however, large-scale epidemiologic surveys of the incidence of mental disorders are less common. The ECA study, which has as one of its goals a follow-up of previously examined respondents, represented one of the first attempts at determining the annual incidence of specific disorders in a large, representative sample of a demographically diverse population.

Incidence estimates for the ECA study at 1-year follow-up per 100 person-years are 1.8% for alcohol abuse or dependence, 1.1% for substance abuse or dependence, 1.6% for major depression, and 4% for phobias (44, 45). Estimates from the NEMESIS were generally higher (46), 2% for alcohol abuse and 3.1% for major depression. In Edmonton, the annual incidence of alcohol dependence was 4.48% in men and 1.2% in women. The incidence of major depression was 1.96% in men and 3.72% in women (47). Three-year incidence rates from the NESARC per 100 person-years were 1.7% for alcohol abuse or dependence, 0.3% for drug abuse or dependence, 2.2% for any mood disorder, and 1.6% for any anxiety disorder (48). In general, these incidence rates indicate a substantial generation of new cases in a 1-year period of a magnitude reaching almost half the 1-year prevalence for some diagnoses (e.g., phobia). Conversely, Eaton et al. (44) reported that most 1-year prevalence rates declined between the two interviews, suggesting considerable diagnostic flux in the initiation and remission of active disease. As they noted, a complete picture of the population dynamics of these disorders would require not only reliable incidence and prevalence (1-year and lifetime) rates but mortality data as well.

It is important to note that even given the size of the ECA population, which was unprecedented in psychiatric epidemiology, the number of new cases in most diagnostic categories was relatively small.

When comparing incidence estimates, it is important to consider the age range of the sample and the diagnostic criteria in place at the time the survey was conducted. For example, the annual incidence of major depression in the NEMESIS sample is higher than in the ECA sample, which may be attributed in part to the NEMESIS excluding participants who were 65 years or older (a group with a lower incidence of major depression than younger adults). However, the incidence estimates differ between the ECA and Edmonton samples, two studies with similar age groups and the same diagnostic criteria. In summary, these studies suggest variability in the incidence of psychiatric disorders.

32.5. Comorbidity

Community epidemiologic studies also allow us to examine the comorbidity of psychiatric disorders. In the ECA, all disorders except cognitive impairment had prevalence rates of at least one additional diagnosis of over 50%, with four categories (somatization, antisocial personality disorder, panic disorder, and schizophrenia/schizophreniform) having over 90% comorbidity (14). The strongest statistical associations included schizophrenia with mania and panic disorder; depression with mania, panic disorder, and somatoform disorder; and antisocial personality disorder with alcohol and drug abuse/dependence. Robins et al. (14) suggest that because relatively few disorders share symptoms as diagnostic criteria or risk factors, the most likely reason for this co-occurrence is that having one disorder increases the risk of developing a second disorder, which may imply a causal relationship. Further investigation of age of onset of each disorder is needed to determine the direction of causation.

In the NCS, 52.0% of the sample did not have a lifetime disorder, 21.0% had one disorder, 13.0% had two disorders, and 14.0% had three or more lifetime disorders (5). A total of 58.9% of the 12-month disorders and 89.5% of the severe 12-month disorders occurred in those with a lifetime history of three or more disorders. The NCS investigators conclude the major burden of psychiatric illness is concentrated in a smaller group of individuals (14% of the sample) (5). In the NCS-R, 14.4% had one disorder, 5.8% had two disorders, and 6.0% had three or more disorders in the past 12 months (35).

In the NEMESIS, 4.4% met criteria for two or more disorders in the previous 12 months (42). In the C-MHS, the 12-month prevalence of any disorder was 7%, a proportion lower than observed in the NEMESIS. A total of 5.4% had exactly one disorder, 0.9% had exactly two disorders, and 0.7% had three or more disorders. The majority of cases identified as severe were among those with two (35.4%) or three (23.4%) 12-month disorders. By contrast, 62.9% of those with a mild disorder were among those participants who met criteria for exactly one disorder (40), findings similar to those reported from the NCS.

32.6. Use of Mental Health Services

In the ECA data, relatively few persons suffering from most specific current diagnoses had used mental health services. The overall rate of use of mental health services for all disorders was 13% for those with a single diagnosis and 19% for all respondents with one or more diagnoses (14). In the WHO World MHS, disorder severity was correlated with probability of treatment.

However, in developed countries, 35.5–50.3% of serious cases received no treatment in the 12 months prior to the interview. The percentage is much higher in less-developed countries (76.3–85.4%). In the USA, using data from the NCS-R, 52.3% of those with a disorder in the previous 12 months classified as "severe" received treatment, whereas 34.1% of those with a "moderate" disorder and 22.5% of those with a "mild" disorder received healthcare treatment. Use was much less in the M-NCS, with only 20.2% of people with severe disorders using services (7). These data consistently show that a significant number of persons in the community with a psychiatric disorder do not receive treatment.

Racial/ethnic disparities in care may persist. For example, in the CPES, a total of 51% of adults meeting 12-month criteria for major depressive episode received depression care. While 54% of non-Latino whites received care, only 40% of African Americans, 34% of Mexican Americans, and 29% of Caribbean blacks received care. These disparities persisted for both psychotherapy and pharmacotherapy (49). In the NASL, only 31.9% of African American and Caribbean blacks with a 12-month DSM disorder used some form of mental health services (10).

32.7. Etiology of Psychiatric Disorders

Psychiatric disorders may derive from biological, psychological, and social causes (and even spiritual causes). Epidemiologic studies have enhanced our understanding of the relative contribution of each of these potential causative factors. The multiple causes of psychiatric disorders should not be viewed as competing but rather as complementary and almost always transactional. For example, if an individual is vulnerable to social stressors, this vulnerability may originate from underlying biological mechanisms that interact with social factors.

For the remainder of this chapter, we will present examples of biological, psychological, and social risk factors that contribute to the etiology of psychiatric disorders that have been discovered or substantiated from epidemiologic studies (predominantly community-based epidemiologic studies). We divide the review into biological, psychological, and social origins more for convenience of organization than to suggest that these domains cannot be connected theoretically or demonstrably. We stop short of proposing an overall model that integrates all potential causative factors. Finally, we do not discuss the demographic differences in the frequency of psychiatric disorders, such as the increase of major depression among women compared to men and the lower frequency of major depression among community-dwelling elders compared to younger adults (which we have documented earlier in this chapter). Finally, no chapter of reasonable length can provide an in-depth review of all relevant studies. Therefore, we review a group of representative studies to illustrate the value (and limitations) of epidemiologic studies exploring the etiology of psychiatric disorders.

32.7.1. Biological Origins

Studies of biological origins of psychiatric disorders substantiated by community-based epidemiologic studies may be divided into several broad categories. The first category consists of the epidemiologic studies that identify inherent risk for the development of psychiatric disorders. Perhaps the most extensive epidemiologic studies that identify inherent risk are studies of genetics and heredity. For example, studies of older adults in Scandinavia have identified that genetic influences account for approximately 16% of the variance in total depression scores using the Center for Epidemiologic Studies Depression Scale (CES-D) and 19% of the variance in somatic symptoms within the CES-D (50).

Twin studies have also been very helpful in identifying the familial risk for schizophrenia. In one study from Norway, the concordance of schizophrenia in a second twin when the first twin was diagnosed with schizophrenia approached 48% for monozygotic twins compared to 4% in dizygotic twins (51). Adoption studies have also helped clarify the role of genetic and environmental factors in the transmission of schizophrenia. For example, a study in Copenhagen identified 34 adoptees diagnosed with schizophrenia. These adoptees were separated from their biological parents at an early age and raised by parents with whom they had no biological relationship. Schizophrenia and related psychiatric disorders were more likely to be found in the biological relatives of the schizophrenic adoptees than in the adoptive parents (52).

A second broad category consists of those studies which identify potential external biological risks for psychiatric disorders. An example of such a study may provide yet another clue to the biologic causation of schizophrenia. This historical cohort study explored the impact of a severe famine during the Dutch Hunger Winter of 1944–1945 (53). The caloric restriction, which resulted during World War II in the Netherlands, resulted in many deaths, decreased fertility, increased mortality, and low birth weights. The famine was time limited, and therefore, children exposed to the famine could be compared with children who received adequate caloric intake. Exposure during the peak of the famine while children were still in utero increased the risk of schizophrenia at the least twofold. Such studies, however, are only suggestive.

Another category of research is the area of gene and environment interaction. That is, people exposed to the same environmental risk may differ in their response, suggesting genetic susceptibility may play a role. For example, the serotonin transporter gene 5-HTT may contribute to stress response (54).

32.7.2. Psychological Origins

A number of psychological factors may contribute to the onset and progression of psychiatric disorders. Three psychological constructs will be described as examples. The first is personality attributes. Neuroticism may set in motion processes that lead to disorders. Neuroticism and mental disorders may share common risk factors, or neuroticism and mental disorders may be manifestations of the same process (55). Characteristics of neuroticism include anxiety, a tendency toward self-pity, tension, frequent worry, and an impulsive as well as unstable lifestyle. Major depression, in one study of older adults, was much more likely to occur in the presence of a combination of ongoing daily hassles and a high level of neuroticism. This association was found to increase risk for depression even when there was no documentation found for a stressful life event (56, 57).

Temperament, another psychological construct, has been associated with the onset of psychiatric disorders. Concepts of temperament emphasize its emotional, motivational, and adaptive aspects. Temperament may be defined as a constitutional disposition to react to one's environment in a particular way. For example, some individuals enjoy novelty and are likely to take more risks. Others are more anxious, rigid, and compulsive and therefore attempt to avoid situations that they perceive may increase their exposure to harm. Many scales have been developed to assess temperament, and these scales can be included in psychiatric epidemiologic studies. In a Japanese study, an anxious temperament was associated with an increased risk of early onset generalized anxiety disorder, especially in women (58).

Cognitive distortions, a third psychological construct, have been proposed by Beck (59) as a cause of depression across the life cycle. In theory, the depressed may overreact to life events as well as misinterpret events and exaggerate their potential for an adverse outcome. In one study, subjects with a higher frequency of depressive symptoms tended to use acceptance, rumination, and catastrophizing to a higher extent and to use positive reappraisal to a lower extent than those who had fewer depressive symptoms. We do not know, however, whether these cognitive distortions predispose to the development of depression or whether they simply accompany the development of depression. For this reason, epidemiologic studies that demonstrate an association between psychological factors and psychiatric disorders at one point in time cannot be used to definitively establish a causal relationship between psychological factors and the psychiatric disorder (60).

32.7.3. Social Origins

The most common proposed pathway by which social factors contribute to psychiatric disorders involves the stress (negative impact on an individual) resulting from environmental stressors. Stress may be defined as that condition of an individual during which energy is continually being used to cope with external problems. Stress may either be intermittent, as with stressful life events, or continuous. Stressful life events may include extreme traumatic experiences such as being the victim of physical or psychological abuse or losses such as the loss of a loved one.

The continuous stress of deployment to Iraq among soldiers is associated with neuropsychological symptoms including confusion, difficulty maintaining attention, verbal learning, and visual-spatial memory (61) as well as associated with an increased risk for psychiatric disorders including major depression and posttraumatic stress disorder (62). These war zone service effects may be persistent or even increase over time (63). One possible mechanism by which either stressful life events or chronic stress may lead to the onset and persistence of psychiatric disorders is through the neuroendocrine system. For example, chronic stress is known to disrupt the body's (and brain's) homeostasis (64). In addition, chronic stress seems to increase exposure of the brain to higher levels of norepinephrine as well as cortisol (and elevated cortisol levels are associated with shrinkage of the hippocampus) (65, 66). Many social stressors have been associated with an increased frequency of psychiatric disorder in community-based epidemiologic studies. Some of these factors are described below, and examples of studies demonstrating these associations are briefly described. Although the association of social factors with psychiatric disorders is well established via epidemiologic studies, the mechanisms by which social factors contribute to psychiatric symptoms are poorly understood.

32.7.3.1. Stressful Life Events

Childhood trauma has been linked to increased risk for the onset of psychiatric disorders in adulthood, as detailed in retrospective studies. The NCS-R data suggests childhood adversity may be associated with 44.6% of all childhood onset disorders and 25.9–32% of late-onset disorders (67). Parental loss through death or separation has been associated with depression,

agoraphobia with panic attacks, and generalized anxiety disorder (68). Studies have also suggested that childhood trauma may be associated with neuropathological findings that are known to be associated with psychiatric disorders, such as hippocampal damage (69, 70). Childhood adversity is also associated with increased vulnerability to the mental health effects of adult stressors in both men and women (71). Severe trauma in adulthood has also been associated with the development of psychiatric disorders. For example, environmental distress, such as the Three Mile Island nuclear accident, was associated with both major depression and generalized anxiety (72). Sexual assault has been found to increase the risk of major depression as well as alcohol and drug abuse up to threefold (73). In the English 2007 Adult Psychiatric Morbidity Survey, the effect of work stressors on common mental disorders was not explained by coexisting nonwork stressors, suggesting both contribute (74).

Traumatic events can be buffered by both personal and social factors. For example, among Vietnam veterans who reported both having support from family and friends at their homecoming and having current social support, symptoms of posttraumatic stress disorder were lower (75).

32.7.3.2. Socioeconomic Status

Low social economic status using indices of education, occupation, and income has long been associated with psychiatric disorders (76, 77). Use of mental health services by the severely and chronically mentally ill has consistently been inversely related to social economic status. However, these findings must be evaluated critically, for the relationship may not necessarily be unidirectional. The location of subjects may contribute to the increased risk of schizophrenia related to low socioeconomic status. For example, the discrepancy between socioeconomic status and schizophrenia may largely be a phenomenon of large cities (78). A second theory suggests that socioeconomic status does not necessarily cause schizophrenia but rather that schizophrenia and its debilitating effects upon social function lead to downward mobility in socioeconomic status (79). Not all studies, however, are positive. Findings in controlled analysis from the NCS-R did not support the association of family income with an increased frequency of psychiatric disorders (35). These investigators did find, however, that less than a high school education was associated with an increased frequency of some disorders.

32.7.3.3. Occupation

Although there have been few studies that convincingly demonstrated an association between specific occupations and an increased risk for psychiatric disorder, many studies have documented the increased frequency of psychiatric disorders among the unemployed. For example, the overall prevalence of psychiatric disorders among the unemployed in the ECA study was 48% for lifetime diagnoses and 29% for current diagnoses, a frequency much higher than for individuals who were employed (14). This increased frequency among the unemployed held true for schizophrenia, major depression, alcohol abuse and dependence, obsessive-compulsive disorder, somatization, and antisocial personality disorder. In the CPES, among both whites and Latinos, being out of the labor force was associated with the prevalence of depression (80). In addition, epidemiologic studies have shown a consistent association between work-related stress and psychiatric disorders (81). For example, in Norway, physicians have higher suicide rates than the general population (82). Similar work has shown most of the variation in suicide risk across occupations is explained by the social and economic characteristics of the people in the occupations (with the exception of higher rates for doctors and nurses due in part to their increased risk of self-poisoning) (83).

32.7.3.4. Marital Status

Marital status has been associated with frequency of psychiatric disorders in a number of ways. One report from the ECA study found the frequency of psychiatric disorders to be highest among separated (26.7%) and divorced (25.8%) people, followed by the never married (21.5%) (84). When evaluated by sex, the rate among men was highest among the widowed, separated, and divorced (30.4%), whereas rates for women were highest among singles (21.4%). Relationship with one's spouse, however, showed a strong correlation with prevalence. Subjects who reported poor marital relationships were found to have a 51.2% frequency of psychiatric disorders versus a frequency of 21.4% among subjects who reported fairly good relationships and 12% among subjects with very good relationships. The risk for schizophrenia is about four times higher among individuals who have never married when compared with the married (85). This finding, however, is probably due to the early onset of schizophrenia, which decreases the likelihood of marriage. In the WHO World MHS, being married was associated with a reduced risk of first onset of most mental disorders for men and women. Being previously married was associated with an increased risk for both genders (86).

32.7.3.5. Impaired Social Support

Social support consists of many factors, including perception of the social network, actual individuals within the social network, as well as the tangible help and assistance available from the social network (87). The strongest association between impaired social support and psychiatric disorders, especially depression, has been found with perception of support. For example, in a community study from Hong Kong, impaired social support and depressive symptoms were positively associated (including network size, network composition, social contact frequency, satisfaction with social support, and instrumental-emotional support) (88). In a Dutch study, feelings of loneliness rather than social isolation were found to be a major risk factor for mortality in older men. Neither loneliness nor isolation, however, was associated with mortality in older women (89). Social support can mediate between these factors and the onset of psychiatric disorders. In one study, perceived social support was employed to mediate the association between disability and depressive symptoms over time among older adults (90). In another study of older adults, the effect of stress on an incident depression was modified by factors from the environment including marital status and social support (91).

32.7.3.6. Urbanization

In the North Carolina site from the ECA study, the frequency of major depression as well as agoraphobia and panic disorder was nearly two times as high in the urban setting compared with the rural setting (92). Urbanization has often been theorized to be a risk factor for psychiatric disorders. An early study in Nova Scotia proposed that psychiatric disorders were more frequent in disintegrated social settings compared with integrated social settings (93). Small rural communities were postulated to be more integrated and therefore protective against the onset of psychiatric disorders. Findings from the NCS-R confirmed the slight increased risk of more severe psychiatric disorders in urban compared to rural settings (35).

32.7.3.7. Immigration

There may be differences in the risk of psychiatric disorders by immigration status. In the NESARC, both foreign-born Mexican Americans and foreign-born non-Hispanic whites had a significantly lower lifetime prevalence of DSM-IV substance use, mood, and anxiety disorders compared with their US-born counterparts, suggesting potential deleterious effects of acculturation on psychiatric morbidity in the USA (94). This immigrant paradox, however, may not apply equally to all Latino groups and to all psychiatric disorders (95). In addition, there may be differences by country of origin and age at immigration. In the NESARC, foreign-born adults from Mexico, Eastern Europe, Africa, or the Caribbean who arrived in the USA at age 13 or older had a lower risk for mood and anxiety disorders compared to those born in the USA, but immigrants who arrived prior to age 13 did not differ in their risk. There was no association between US birth and disorder risk among people from Western Europe or Puerto Rico (96). Another study reported that the increased risk associated with migration from Mexico to the USA was particularly strong in recent birth cohorts (97). Finally, recent research in Canada examining contextual effects found the risk of 12-month psychiatric disorders among Canadian immigrants further decreased as neighborhood immigrant concentration increased (98).

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33
Suicide and Attempted Suicide

J. John Mann, M.D. and Dianne Currier, Ph.D.

Abstract The Global Burden of Disease project estimated 782,000 lives were lost through suicide worldwide in 2008 (1). In the United States, in 2010, 38,364 individuals died by suicide making it the tenth leading cause of death. Men are four times more likely than women to die by suicide; however, women make more nonfatal suicide attempts than men. There are many contributory factors to suicide and suicide attempts, the most important of which is having psychiatric disorder. Over 90% of suicides have a diagnosable psychiatric disorder at the time of their death, the most common being mood disorders. Other disorders with increased risk for suicidal behavior are psychotic disorders, alcohol and substance use disorders, and personality disorders, particularly Cluster B personality disorders. Other risk factors for suicide and suicide attempt include a family history of suicide and suicide attempt, a history of previous suicidal behavior, aggressive/impulsive traits, hopelessness and pessimism, a history of childhood abuse, head injury, and access to lethal means such as firearms.

Assessing a suicidal patient involves evaluating current stressors as well as assessing enduring risk factors and indicators that an individual has a propensity to engage in suicidal behavior when under stress. Stressors include current life events or an episode of psychiatric illness, particularly a depressive episode. Longer-term risk factors include aggressive and impulsive traits, trait pessimism, and a history of past suicidal behavior because it indicates a predisposition to suicidal acts. Individuals who present with severe suicidal ideation, a specific plan for suicide or express intent to suicide, and who have ready access to lethal means are at high risk and require immediate intervention, up to and including hospitalization. Long-term treatment strategies should also include addressing enduring risk factors.

Keywords Suicide · Attempted suicide · Risk factors · Prevention · Major depression

33.1. Suicide and Attempted Suicide

33.1.1. Demographics

Worldwide, in 2008, an estimated 782,000 lives were lost through suicide, representing 1.5% of the global burden of disease and ranking in the top 20 of causes of years of healthy life lost through premature death or disability (1). In the United States, in 2010, suicide was the tenth leading cause of death and accounted for 38,364 deaths, an age-adjusted death rate of 12.1/100,000

J.J. Mann, M.D. (✉)
Paul Janssen Professor of Translational Neuroscience, Department of Psychiatry, Columbia University, Chief, Department of Neuroscience, New York State Psychiatric Institute, New York, NY, USA
e-mail: jjm@columbia.edu

D. Currier, Ph.D.
Senior Research Fellow, Centre for Molecular, Environmental, Genetic and Analytic Epidemiology, Melbourne School of Population Health, The University of Melbourne, Carlton, Victoria, Australia
e-mail: dianne.currier@unimelb.edu.au

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(2). From 1990 to 2000, the overall suicide rate declined from 12.4/100,000 to 10.7/100,000 (3). However, the 2010 suicide rate is comparable to suicide rate in 1950 of about 12/100,000. Suicide remains the third leading cause of death in the 15–24 year's age group despite a 21% decline from 1990 to 2000 (13.2 down to 10.5/100,000) and then an uptick that persisted to the present after the introduction of the Food and Drug Administration (FDA) black box warning on antidepressants and their potential effects on risk for suicide (2). The suicide rate in 15–24-year-olds was 10.5/100,000 in 2010. Disproportionally high suicide rates are also found among males over the age of 65, namely, 28.4/100,000 (4). In the United States, men die by suicide over four times more frequently than women (males 18.5 vs. females 4.7/100,000 in 2007), and white Americans are more than twice as likely to die by suicide than African Americans (12.6 and 4.9, respectively, in 2007) (5). In 2010, there were 30,277 male suicides and 8,087 female suicides (2). Of note, there has been a relative rise in suicide rates in middle age in the last 5 years, and now the rate in the 45–54 year's age group is the highest of any age group at 19.8/100,000 in 2010 (2).

Suicides may be underreported or underestimated due to medical examiner or coroner experience and practice and social factors such as stigma. Opinions differ as to the magnitude of the underestimation, ranging from 10 to 50% (6). Most of the missed cases of suicide are reported in the category of cause undetermined. Holding and Barraclough found that missed cases are descriptively more like suicides than like accident victims (7). The achievement of uniformly high-quality ascertainment practices would increase the number of suicides identified.

Official statistics are not gathered on suicide attempts, and there is no national registry in the United States, however, it is generally estimated that there are 8–25 suicide attempts for each suicide. US national epidemiological data indicate that there are approximately 500/100,000 suicide attempts per year, which is a ratio of approximately 50:1 attempts to suicides (8). The ratio of suicide attempts to suicides varies considerably across age groups with reported ratios in adolescents of up to 87:1 and in adults over 65 years of age only 4:1 (9, 10). It has been estimated that 678,000 individuals report receiving medical attention for a suicide attempt per year in the United States. Rates of nonfatal attempted suicide are about three times higher in women compared with men (11).

33.1.2. Defining Suicidal Behavior

Suicidal behavior encompasses suicidal ideation, nonfatal suicide attempts of varying intent and lethality, and suicide. The Institute of Medicine in the United States defines suicidal behavior as follows:

- Suicide: fatal, self-inflicted destructive act with explicit or inferred intent to die.
- Suicide attempt: a nonfatal, self-inflicted destructive act with explicit or inferred intent to die.
- Suicidal ideation: thoughts of harming or killing oneself (12).

Suicide attempts vary in both lethality and intent. Lethality is the degree of medical damage resulting from a suicide attempt, and suicidal intent concerns the degree of preparation involved and the chances of discovery or rescue. More highly lethal attempts usually involve more careful planning including taking measures to avoid detection and the use of more lethal methods such as firearms. Surviving such an attempt is often the result of good fortune, and the term "failed suicide" has been used to describe this group, which demographically, biologically, and in terms of suicide intent resemble completed suicides (13–16). Lower lethality attempts are more often impulsive, usually occur in the context of a social crisis, and often have a strong element of appeal for help insofar as they are carried out in a manner that favors discovery and rescue. Higher lethality attempts are more common in men, as is suicide, whereas women tend to use less lethal suicide methods with a higher chance of survival (12). Thus, differences in the degree of intent and lethality distinguish different types of suicide attempts.

Suicidal ideation refers to thoughts of harming or killing oneself, and the frequency, intensity, and duration of such thoughts can vary considerably. Suicidal ideation without action is more prevalent than attempted suicide or suicide. In the United States, the estimated rate of suicidal ideation is 2.8–3.3% of the general population (8), and between 2 and 18% across nine countries (11). In the United States, the annual prevalence rate of suicidal ideation in youth is closer to 20%, and the annual rate of medically serious suicide attempts is over 2%.

Suicide and attempted suicide are complex behaviors with multiple contributory factors and causal pathways. Models of suicidal behavior can provide an explanatory framework and contextualize the various risk factors and may facilitate the assessment of suicide risk. One such model of suicidal behavior is the stress–diathesis model, which proposes that individuals who have a diathesis, or predisposition, for suicidal behavior are more likely to engage in a suicidal act when confronted by a stressor (16). Stressors might include an episode of psychiatric illness or stressful life events such as relationship difficulties or unemployment. The diathesis is thought to be characterized by a tendency for pessimism, aggressive/impulsive behavioral traits, impaired problem solving, and cognitive rigidity and all these facets have genetic and biological underpinnings (17, 18).

33.2. Neurobiology of Suicidal Behavior

Alterations in a number of neurotransmitter systems and neural circuits have been associated with suicide and/or attempted suicide. More generally, observed changes in neurobiology at a cellular or circuitry level may be associated with a primary psychiatric disorder, or they may relate to the diathesis for suicidal behavior, or they may be indicators of excessive stress experienced in the period leading up to a suicidal act.

Specific types of impairments of the serotonergic system have been consistently reported in suicides and suicide attempters across different psychiatric diagnoses, indicating that these biologic changes are related to the suicidal behavior and not to any one psychiatric disorder (see Mann (19) for a review). Serotonin impairment associated with suicidal behavior appears to be a trait and hence can predict future behavior and correlates with lethality of past suicidal behavior (20, 21). A meta-analysis of prospective studies of 5-hydroxyindoleacetic acid (5-HIAA), the major metabolite of serotonin found in the cerebrospinal fluid (CSF) and a guide to serotonin activity in parts of the brain including the prefrontal cortex, found that depressed patients with low CSF 5-HIAA had a more than fourfold risk chance of dying by suicide (22). One mechanism through which serotonergic dysfunction might relate to suicidal behavior is via the impulsive/aggressive traits that are a component of the diathesis for suicidal behavior. A second mechanism is through recurrent mood disorders since low serotonergic function appears to be a trait in mood disorders (23, 24). Postmortem studies of the brains of those who died by suicide have observed abnormal serotonergic function localized to the ventromedial prefrontal cortex (25–27), a region of the brain involved in the executive function of behavioral and cognitive inhibition (28) and therefore decision-making. Diminished serotonergic input into this part of the brain may contribute to impaired inhibition and thus create a greater propensity to act on suicidal or aggressive feelings. Brain imaging studies have linked prefrontal cortical activity and serotonin release to suicide attempts (29) and impulsivity (30). Low uptake of 11-C-methyltryptophan, an analogue of tryptophan the essential amino acid precursor of serotonin, observed in the ventral prefrontal cortex of higher intent suicide attempters (31) supports these postmortem and imaging findings. In depressed suicide attempters, lower CSF 5-HIAA is associated with greater aggression and hostility. Interestingly among suicide attempters, only those who make more highly lethal attempts have a lower CSF 5-HIAA indicating a serotonin deficit comparable to completed suicides, whereas low lethality attempters have CSF 5-HIAA levels comparable to non-attempters (14, 32).

Abnormalities in the noradrenergic system and the hypothalamic–pituitary–adrenal (HPA) axis have also been associated with suicidal behavior (for a review see Mann (19)). Both systems are related to stress response, and dysfunction in these systems appears to be both state dependent and indicative of an enduring trait of hyper-reactivity to adult stress and, therefore, part of the diathesis. A sensitization of the two major stress response systems has been shown in rodent studies to result from maternal deprivation in infancy (33, 34).

There are fewer noradrenergic neurons in the rostral or upper locus coeruleus in the brainstem in depressed suicide victims, and they are the subset of noradrenergic neurons that project to the brain as opposed to the spinal cord (35), along with indications of cortical noradrenergic overactivity such as lower alpha- and high-affinity $beta_1$-adrenergic receptor binding (36). More recently, we have reported that low CSF MHPG, a major metabolite of norepinephrine, can predict both the probability of suicide attempts in depressed patients and the lethality of those suicide attempts (37). This suggests that part of the diathesis for suicidal behavior is a lower noradrenergic neuronal mass combined with a sensitization of the stress response due to childhood adversity, such that an adult stress results in excessive release of norepinephrine (NE). Since the neuronal population is already smaller, the excessive release of norepinephrine increases the risk of depletion. Rodent studies suggest that helplessness and giving-up behavior results from NE depletion and those behaviors are seen to be in excess in suicidal behavior.

Suicidal patients in diagnostically heterogeneous populations exhibit HPA axis abnormalities, most commonly resistance to dexamethasone challenge (38–46). A meta-analysis of prospective studies of HPA axis dysfunction and suicide reported a 4.6-fold increase in risk for dexamethasone nonsuppressors (22). Suicides with a reported childhood history of abuse differ from controls and from suicides without a history of childhood abuse in having greater methylation of CpG sites that affect gene expression of the glucocorticoid receptor gene and less expression of that gene (47). This receptor mediates the feedback inhibition of the cortisol response to stress. This enhanced DNA methylation and reduced expression has also been observed in maternal-deprived mice where it persists into adulthood from infancy and is associated with excessive corticosterone release in response to air puff startle in adulthood (48). This may form the molecular mechanism for childhood adversity resulting in dexamethasone resistance and excess cortisol responses to stress in adulthood. How that in turn increases suicide risk is less certain but may involve effects on mood stability and on cognitions related to problem solving and decision-making.

Other biological systems being investigated with respect to suicidal behavior include fatty acids (49), cholesterol (50), and neurotrophic factors such as BDNF (51).

33.3. Heritability of Suicidal Behavior

Suicide and nonfatal suicide attempts cluster in families of individuals who commit suicide or make suicide attempts (52–56). This is the case in comparison to both general population controls and to families of psychiatric controls who have never attempted suicide. A meta-analysis of 22 controlled family studies covering both suicide attempt and suicide found a nearly threefold overall increased risk of suicidal behavior among close relatives of suicidal versus non-suicidal individuals (57). Suicidal behavior is transmitted in families in part independently of the transmission of mood disorders and other major psychiatric syndromes (58).

How is suicidal behavior transmitted in families? One mechanism is via the diathesis or predisposition to suicidal behavior. Familial factors may contribute to the development of the diathesis for suicidal behavior through both genetic and environmental effects on brain and behavior development, as well as acting as more immediate stressors. Evidence of a genetic contribution comes from twin studies which have shown a higher concordance rate for both suicide (59) and suicide attempts (60) in monozygotic versus dizygotic twins. Pooled data from seven twin studies found the overall concordance for suicide or suicide attempt was 23.5% in MZ twin pairs versus 0.13% in DZ twins (57). Twin studies indicate that genetic factors predict 17–45% of the variance in suicidal behavior (61, 62) and individual and shared environmental influences together accounted for 35–75% of the variance (63). Adoption studies further support a role for genetics in liability for suicidal behavior, documenting higher rates of suicide in the biological parents of adoptees who commit suicide, compared to biological relatives of non-suicidal adoptees (64). There is more than fourfold greater risk for suicide among biological relatives compared with adoptive relatives of individuals with psychiatric disorders who had died by suicide, although in one study this was not the case for suicide attempt, perhaps due to the variability of lethality and intent of suicide attempts affecting degree of genetic effect (65). A large Australian twin study found a genetic contribution to suicide attempts and even suicidal ideation (62). In general, the heritability of suicide is comparable to the heritability of other major psychiatric disorders such as bipolar disorder and schizophrenia (62).

33.3.1. Pathways for the Family Transmission of Suicidal Behavior

Family (66) and twin (62) studies find little evidence that the familial transmission of suicidal behavior is due to imitation or modeling. Rather, a combination of genetic and environmental factors influencing brain and personal development is the likely pathway for the familial transmission of suicidal behavior.

Candidate genes for suicidal behavior have been selected largely on the basis of established biological correlates of suicidal behavior. Thus, genetic studies have focused primarily on the serotonergic system and include genes related to the serotonin transporter, serotonin 5-HT_{1A}, 5-HT_{1B} and 5-HT_{2A} receptors, monoamine oxidase A (an enzyme responsible for the degradation of serotonin), and tryptophan hydroxylase 1 and 2 (TPH1, TPH2), the two rate-limiting biosynthetic isoenzymes for serotonin (see Mann (67) for a review).

These genetic studies have mostly been association rather than linkage studies and have produced inconsistent results (see Baldessarini and Hennen (57) for a review). A meta-analysis of 14 serotonin 5-HT_{2A} receptor gene and 12 serotonin transporter gene association studies found that there was an association between the low expressing variant of the serotonin transporting gene promoter (5-HTTLPR) and suicide, but no such association for a 5-HT_{2A} receptor 102 T/C polymorphism (68). Promising associations between the A218C polymorphism in the tryptophan hydroxylase 1 gene, suicide attempt behavior, and lower serotonergic function have been reported, although not all studies agree (see (67) for a review). The TPH1 gene expresses a form of TPH found in the pineal gland and outside the brain except for a phase in early development. TPH2, a more recently discovered gene, is expressed in the brain; and preliminary studies link an intronic polymorphism to suicide and depression (69). We found another polymorphism associated with a truncated transcript that does not include the catalytic site of the enzyme, was associated with MDD but not suicide (70). Other genetic studies investigate associations between genes and behavioral phenotypes related to suicidal behavior such as aggression and impulsivity (see Courtet (71) for a review). Promising associations have been found for a functional MAOA gene promoter variant (MAOP) and violent and impulsive behavior, particularly in men (71, 72).

Recent genetic studies suggest that it is the interaction between genetic vulnerability and environmental conditions that increases the likelihood of developing a diathesis for suicidal behavior. Adverse childhood experiences in combination with a lower expressing variant of the MAOA gene contributed to the development of antisocial behavior and more impulsivity (risk factors for suicidal behavior) in males but not females (73, 74). There is debate whether the lower expressing allele of the serotonin transporter gene interacts with childhood adversity to increase risk for both depression and suicidality in response to stressful life events in adulthood (75, 76).

Suicide and suicide attempt are complex behaviors and likely to be polygenically determined phenomena. Emerging genetic research techniques such as microarrays and SNP chips evaluate association of thousands of genes with disease and may further identify relevant genes. Larger-scale genome-wide association studies (GWAS) (77–80) have generally failed to find gene

associations that survive correction for the false discovery rate, their best candidates are not generally replicated across these studies, and these studies are not confirming any of the major candidate genes identified from the known neurobiological abnormalities associated with suicide and suicidal behavior. GWAS followed by microarray findings rather than another GWAS population replication may be useful to identify candidate genes for suicidal behavior such as genes related to the inflammasome (81). Other studies using convergent approaches (gene expression and genotyping) have found suicidal behavior associated with genes related to polyamines such as spermidine/spermine N1-acetyltransferase 1 (SAT1) (82, 83).

33.4. Risk Factors for Suicidal Behavior

33.4.1. Psychiatric Disorder

Suicide is a rare event, occurring only slightly more than once among 10,000 persons annually in the United States. Prospective studies of suicide are thus difficult to mount because of the large sample size necessary to achieve adequate statistical power. An alternative strategy is psychological autopsy studies. This type of investigation arrives at a diagnosis in a suicide by ascertaining information on psychopathology from interviews with family members, attending physicians, and others, as well as by reviewing hospital and other official records (84). Diagnosis by psychological autopsy has proven to be reliable and valid (85). To avoid selection bias, it is best to study a consecutive and therefore unselected series of cases. Most psychological autopsy studies that investigate clinical and other factors beyond diagnosis adopt a case–control approach.

Over 150 psychological autopsy studies have been conducted since the early 1960s. A review reported rates of psychiatric disorder in suicides as 91% (ranging from 23 to 100%) in case series reports and 90% (ranging from 86 to 97%) in case–control studies (86). When a psychiatric diagnosis has not been made, it may be because suicides had psychopathology not captured on standard assessment instruments such as the SCID I or SADS, for example, diagnoses included pathological gambling or Axis II disorders, or symptoms and signs may have been subthreshold (87). Alternatively, the families may not have known enough about the suicide, especially closer to the time of death, and so the data are missing. Most studies find about 90% of suicides have a diagnosable psychiatric disorder at the time of death (86), although there are exceptions to these findings. For example, in a Chinese psychological autopsy study, 37% of suicides had no psychiatric disorder (88). This high number was largely due to a high number of impulsive attempts carried out in the context of acute interpersonal conflict using highly lethal pesticide ingestion. Such cases are the exception however, and psychiatric illness is a key causal factor in suicidal behavior.

Psychological autopsies give the proportion of a particular illness among a group of suicides, either a consecutive series or a cohort, but they do not tell us what proportion of individuals with that same illness are likely to die by suicide. Population-based studies are better able to do this and either give a percentage of individuals with a particular disorder who are expected to die by suicide or a standardized mortality rate (SMR) which measures the increase in rate in death by suicide in a certain population, for example, in individuals with a mood disorder, compared to the rate in the general population. SMRs give an indication of the increase in risk of dying by suicide among those with particular psychiatric disorders. Population attributable risk tells us how important as a cause of suicide any specific illness is and that is dependent on the proportion of suicides in that illness and how prevalent the illness is.

33.4.1.1. Mood Disorders

Mood disorders (major depressive disorder and bipolar I and II disorders) are the most frequently observed disorders in psychological autopsy studies of suicide. Reported rates range from 30 to 93% in case series studies and 23–95% in case–control studies (86). Meta-analyses pooling results of individual studies report that a mood disorder diagnosis is found in 30–60% of suicides (86, 89, 90).

Studies of hospitalized cohorts give the rate of suicide in mood disorders as 4–13%, while community samples report lower rates: 2.7% to only slightly higher than general population levels (see Angst (91)). This difference may be a reflection of the practice of hospitalizing patients who are suicidal and thus inpatient samples describe a higher risk group. Angst et al. in a 34-38 year follow-up of hospitalized mood disorder patients reported a SMR of 18 for suicide, that is, an 18-fold higher likelihood of dying by suicide in those patients than in the general population (91).

There is some debate as to the relative levels of risk for suicide in bipolar disorder and major depressive disorder. In a review of 30 bipolar disorder studies, Goodwin and Jamison found that 18.8% of all deaths were by suicide (92). While this rate is higher than the widely cited rate of 7.7% for MDD (93), mortality and psychological autopsy studies report higher risk for death by suicide in MDD than in bipolar disorder. Meta-analysis of follow-up studies with a minimum of 2 years of follow-up calculated SMRs of approximately 20 for MDD and 15 for bipolar disorder (94). More recent large follow-up studies of hospitalized mood disorder patients also report higher SMRs for MDD than bipolar patients (91, 95).

Fewer studies distinguish between bipolar I and bipolar II disorders. A case series psychological autopsy study of 100 suicides found similar rates of MDD and bipolar II disorder (53% and 46%, respectively), but only 1% of suicides had a bipolar I diagnosis (96). However, others found no difference in the SMR for suicide between bipolar I and bipolar II (11.53 and 14.15, respectively) (91). The depressive phase of bipolar disorder appears to carry greater risk for suicide (70–89% of bipolar suicides are in a depressive phase), with elevated risk also in mixed states (dysphoric mania) (11–20%) and negligible risk in mania (97–99).

With respect to suicide attempt, the estimates of rate in bipolar disorder vary. In the Epidemiologic Catchment Area study in the United States, the rates of suicide attempts were 29.2% in bipolar and 15.9% in MDD. A community study of 1,709 adolescents followed until age 30 documented the rate of suicide attempt in bipolar disorder at 44.4% compared to 22% in MDD (100). Both case series and epidemiological studies report the highest suicide attempt rate in bipolar II (24–34%), the lowest in MDD (12–16%) with bipolar I intermediate (17–24%) (101).

33.4.1.2. Psychotic Disorders

Meta-analysis of 38 reports with a combined population of 30,000 schizophrenics found an 8.5-fold greater risk of dying by suicide in schizophrenics compared to the general population (94). Two recent reevaluations of the literature reporting suicide rates in schizophrenics find that 4–5.6% of schizophrenics die by suicide (102, 103), a lower figure than the commonly cited 10–13% (104, 105). Psychological autopsies report 14.1% of suicides have a diagnosis of schizophrenia (19.9% in clinical populations and 7.5% in the general population) (89). Schizophrenia has a higher representation in studies of clinical populations than in community samples (106), as it is a chronic, severe disorder and thus more likely to come to treatment than other disorders. Depression in schizophrenia is a major risk factor for suicidal behavior (107–110) as is substance use disorder (111). Approximately 20–50% of schizophrenics report making a suicide attempt (112).

There are little data available on schizoaffective or other psychotic disorders, and these tend, in psychological autopsy studies, to be grouped together. Rich and colleagues reported seven instances of schizoaffective disorder (3%) under the rubric of "other psychoses" (113), Arato et al. made the diagnosis twice (1%) (114), and Asgard found it in 11 cases, considering it the primary diagnosis in two cases (2%) (115). In meta-analysis, psychotic disorders, excluding schizophrenia, were found in 10.1% of suicides in clinical populations and 2.3% of suicides in the general population (89).

33.4.1.3. Personality Disorders

Personality disorders have come under increasing scrutiny with respect to suicidal behavior. Meta-analysis of psychological autopsies reports 13–16% of cases diagnosed with personality disorders (89, 90). Personality disorders are frequently comorbid with other psychiatric disorders and mortality figures for personality disorders do not always indicate if another disorder was present; thus, it is difficult to ascertain the suicide mortality rate for personality disorder alone. One meta-analysis reported that 3.2% of suicides in the general population had personality disorder as the only diagnosis, but the rate rose to 13% when personality disorder was comorbid with another diagnosis (89). Suicidal behavior in personality disorders is often in context of comorbid major depression and/or alcohol and substance use disorders (116–118). Nevertheless, a personality disorder diagnosis confers a sevenfold increase in risk for suicide (94). Suicide attempt rates are strikingly elevated in some personality disorders, particularly the impulsive/aggressive Cluster B disorders such as borderline personality disorder, where suicide attempt rates of 84% have been reported (119).

33.4.1.4. Anxiety Disorders

Cross-sectional community (120, 121) and clinical studies (122–127) have found associations between anxiety disorders and suicide and attempted suicide. However, there are questions as to what extent this relationship is mediated by comorbid psychiatric disorders, particularly major depression. Lewinsohn and colleagues found, in a community sample of adolescents, that anxiety disorder alone had low rates of suicide attempts, however, when comorbid with MDD, there was a stronger association (128). The association of panic disorder and suicidal behavior appears to be mediated by psychiatric comorbidity, particularly major depression (122, 124–127, 129). An analysis of pooled psychological autopsy results finds anxiety disorders (grouped with somatoform disorders) had an incidence of 2.5% in clinical population suicides and 2.7% in general population suicides (89), however, that rate increases to 6.8% when anxiety disorders are one of multiple diagnoses. Some report that severe agitation or anxiety is associated with increased risk of suicide in mood disorders (130) and others find anxiety is protective against suicide attempts in mood disorders (131).

Post-traumatic stress disorder has been associated, in clinical and community studies, with suicide attempt independently of comorbid major depression or substance use (132–136). The national comorbidity study found that PTSD was the only anxiety disorder independently associated with suicide attempts and ideation (137).

33.4.1.5. Alcohol and Substance Use Disorders

Substance use disorders, particularly alcohol, carry increased risk for suicidal behavior. Meta-analysis of psychological autopsy studies reports alcohol and substance use disorders in 17.6–25% (89, 90). Murphy and Wetzel estimate the lifetime risk of suicide with alcohol dependence in out- and inpatient populations at 2.2% and 4.4%, respectively (138). Based on a meta-analysis, SMRs for suicide in alcohol and substance use disorders are 5.9 and 14–20, respectively, with higher rates for polydrug use (15–44) (94). Alcohol and substance use are frequently comorbid with other high-risk disorders, particularly mood disorders and personality disorders (139). In psychological autopsy studies, comorbid alcohol and substance use disorders and Axis I disorders were present in 23–47% of suicides (86, 89). Acute alcohol intoxication is also a risk factor, and autopsy studies have detected the presence of alcohol in 20–50% of persons who die by suicide (140).

33.4.1.6. Neuropsychiatric Disorders

Increased risk of death by suicide has been reported for Huntington's disease (threefold increase), epilepsy (fivefold increase), traumatic brain injuries (3.5-fold increase), and medical/substance-induced mental disorders (2.5-fold increase), but no increase in suicide risk in dementia (94). That analysis, however, did not take into account comorbidity with major depression or other psychiatric disorders. In psychological autopsies, medical/substance-induced mental disorders as a primary diagnosis were diagnosed in 4% of subjects (141, 142). Meta-analysis found 6.3% of suicides to have medical/substance-induced mental disorders—with 15% in inpatients and 2.1% in the general population (89).

33.4.1.7. Comorbidity

Comorbidity is frequent in psychiatric disorders, and certain comorbidities have been found to increase risk of suicide and suicide attempt. Psychological autopsy studies have found that 70–80% of suicides had more than one psychiatric diagnosis (143, 144). Comorbid mood disorder and substance use disorders were reported in 19–57% of suicides in psychological autopsy studies (86, 89). Substance use disorders also increase the risk of suicide attempt in schizophrenia (145). Suicide attempts are also more frequent in mood disorder patients with comorbid personality disorders, particularly Cluster B personality disorders (146, 147), alcohol and substance use disorders (148, 149), or comorbid PTSD (150).

33.4.2. Special Populations

33.4.2.1. Adolescents

Suicide is the third leading cause of death among young people defined as aged 15–24 years in the United States (5). In 2010, the suicide rate in this age group was 10.5/100,000. This compares with 0.7/100,000 in 5–14-year-olds and 14/100,000 in 25–34 year-olds. Four thousand and six hundred young people died by suicide in 2010. Young men have a suicide rate 5.9 times higher than young women (5). There was a decline in youth suicide rates from about 1990 to 2003, however, following the introduction of a black box warning about suicide risk and antidepressants in youth in 2003, that decline ended and there was an initial uptick in the suicide rate that has since stabilized.

Psychological autopsy studies of smaller samples of 21–53 adolescent suicides report diagnoses of depressive disorder in 51–85%, substance use in 30–62%, conduct disorder in 22%, attention deficit disorder in 26%, and personality disorder in 31% (151–153). In many cases these disorders were comorbid, and Shafii et al. (151) found that 81% of adolescent suicides had more than one diagnosis (151). A larger study of 170 consecutive adolescent suicides using multiple informants found that 91% of cases had a psychiatric diagnosis, with 70% having more than one diagnosis: 61% had a primary mood disorder and 50% a disruptive disorder (144). Thus, the spectrum of psychiatric diagnoses for suicides is similar to adults with regard to mood disorders, but conduct disorder, attention deficit disorder, and substance use disorder are more common and more often comorbid with mood disorders.

Anonymous surveys conducted at high schools indicate that approximately 2% of students have made a suicide attempt that required medical attention, while a larger number made less serious attempts (154). Meta-analysis of population studies comprising 500,000 adolescents found 9.7% (2–30%) reported a suicide attempt, with the rate in females twice that of males (155). Females both in the pediatric age range and in early adulthood make more suicide attempts compared with males. The ratio is reversed for completed suicide.

33.4.2.2. Older Adults

Disproportionally high suicide rates are also found among the elderly. Those over 65 comprise 13% of the US population but account for 20% of all suicide deaths (156). Suicide rates increase with age in males and not females in the United States, and so the male/female ratio for suicide increases over 70 years of age such that older males had a 7.5-fold higher rate of suicide than older females in 2003. In 2010 the suicide rate was 13.7/100,000 for the age group 65–74 years, and in males 65–74 years, the suicide rate was 41.6, and in males over 85, it reached 47.8, whereas for females over 65, it was much lower at 3.8 (2). Consistent with the general decline in suicide rates in the United States since 1990, the suicide rate in those over 65 declined from 17.9 to 11.2% in 2010. A review of ten psychological autopsy studies in older adults 65 years and older found major psychiatric illness in 71–97% of late-life suicides. Major depression was diagnosed in 46–87% of suicides and substance use disorders in 3–43%, but primary psychotic illness and personality and anxiety disorders were not frequently diagnosed, nor was dementia (157). Physical illness is more prevalent in older adults, and prospective studies have found that certain illnesses increase risk for suicide (158). A psychological autopsy found physical illness in 70% of suicides over 60 years (159), however, the extent to which comorbid psychiatric disorders contribute to risk of suicide in those with physical illness has yet to be fully explored and physical illness is just more common in the elderly and may be unrelated to suicide (157).

Attempted suicide is less frequent later in life with a ratio of approximately four attempts for every suicide (9) compared to a ratio of closer to 20 to one in teens or young adults. Older suicides display a greater determination to die, give fewer warnings, and engage in greater planning than younger age groups (160–162). They also are more likely to live alone, reducing chances of detection and rescue.

33.4.3. Other Risk Factors

While psychiatric disorder appears to be a necessary condition of suicide, given that the majority of individuals with psychiatric disorders do not die by suicide, other factors must be involved which increase the risk of suicide. To elucidate these other risk factors for suicide, the most commonly used method is comparison of surviving suicide attempters, particularly those who have made more highly lethal attempts, with individuals who share the same psychiatric diagnosis but have not made suicide attempts. Prospective studies can assess the predictive salience of these correlates for future suicidal behavior. A number of risk factors have been repeatedly identified in retrospective and prospective studies, including aggressive/impulsive traits, cigarette smoking, more severe subjective depression relative to clinician-rated depression, hopelessness, perception of fewer reasons for living, cognitive rigidity, poorer problem-solving capacity, and potential causal factors including a reported history of physical or sexual abuse during childhood, a history of head injury, or neurological disorder.

33.4.3.1. Aggression and Impulsivity

Lifetime aggressive–impulsive traits are more pronounced in suicide attempters compared to non-attempters (163). More severe aggression has been associated with serotonergic dysfunction (164, 165) and there is some indication that aggression may be heritable (66). It is thought that the risk factors for aggression may overlap with suicidal behavior because the two types of behaviors tend to aggregate in the same individuals and share a common abnormality in both serotonin system dysfunction and ventral prefrontal cortical function and structure, a neurotransmitter system and brain region that may underlie behavioral inhibition, or top-down control of aggressive and suicidal feelings. Two recent studies of the serotonin transporter polymorphism found that the lower expressing variant was associated with greater aggressive behavior under stress in men (166) and with more parent- and teacher-reported aggression in middle childhood (ages 8–10) (167). Suicide attempters are more impulsive than non-attempters (18), and disorders which are characterized by high levels of impulsivity, such as borderline and antisocial personality disorders, have higher rates of suicide attempts. Of note, impulsivity is inversely correlated with lethality of suicide attempt (30, 168, 169). Thus, when suicide attempters are more impulsive, they tend to make less lethal attempts, perhaps due to lack of planning and not taking precautions to prevent discovery and rescue. However, the impulsive nature of many suicide attempts does not mean they will not result in death, particularly when highly lethal means are readily available and commonly used, as is the case, for example, with pesticide ingestion in young women in rural China (88).

33.4.3.2. Hopelessness

Beck et al. (170) define hopelessness as "a system of cognitive schemas whose common denominator is negative expectations about the future" (170) (p. 864). In prospective and retrospective studies, hopelessness is associated with more severe suicidal ideation (171–173), suicide attempts (171, 173–177), and suicide (171, 173, 178, 179). Correlation between hopelessness and suicidal behavior has been documented in different age groups including children/adolescents (179–182) and the elderly (183)

and across different psychiatric disorders including mood disorders (174, 176), schizophrenia (177, 184), personality disorders (185), and substance abuse (186) and in community samples (171, 187). It is thought that a tendency to experience relatively greater hopelessness in the face of comparable stressors, such as a depressive episode or a life event, is an aspect of the diathesis for suicide (17).

33.4.3.3. Childhood Abuse

Reported childhood physical and sexual abuse has been associated with suicide attempts in adult depressed patients (188). It is reported that the relationship between abuse and suicidal behavior is largely mediated by psychiatric illness, but a part of the variance remains unexplained by psychiatric syndromes and may be related to the diathesis (189). Childhood abuse increases the likelihood of developing psychiatric illness (190), the main risk factor for suicidal behavior. Preclinical studies have shown that early life adversity has lasting neurobiological consequences, including abnormalities in the serotonergic system (191) and HPA axis stress response (192), both of which have been associated with suicide (22). Moreover, childhood abuse appears to increase the likelihood of developing impulsive/aggressive traits, which also increase risk for suicidal behavior (193).

33.4.3.4. Head Injury

Traumatic brain injury is associated with high rates of psychiatric illness (194, 195), suicidal ideation (194, 196), suicide attempts (195, 197), and suicide (198). Suicidal behavior among those with brain injury is often in the context of depressive disorders, anxiety disorders, and substance abuse or dependence (194), all of which occur at higher rates in the brain-injured population. However, brain-injured individuals in the community have been found to be at higher risk for suicidal behavior after controlling for the presence of a psychiatric condition (195). This may be due in part to increased aggression, as more aggressive individuals tend to have more brain injuries and even mild head injury can increase the risk for aggressive behaviors (197), and greater aggression increases the risk for suicidal behavior. Recent reports of suicides in young retired football players have raised further concerns that milder head trauma can result in an accumulation of tau protein in the brain that has been linked to both suicide and dementia (199).

33.4.3.5. Smoking

Cigarette smoking has been associated with suicidal behavior across diagnostic categories (17) and predicts suicidal behavior in follow-up studies in mood disorder patients (18). The relationship between smoking and suicidal behavior may be, in part, related to neurobiologic abnormalities as decreased serotonergic function has been found among smokers in a diagnostically varied group (200). What remains to be determined is whether smoking shares a common causal factor with suicidal behavior such as low serotonin function and heightened aggressive traits, or whether smoking produces changes in brain function resulting in more aggression and greater risk of suicidal behavior.

33.4.3.6. Life Events and Psychosocial Stressors

Aside from the stressor of an episode of psychiatric illness, life events such as interpersonal and intimate relationship conflict, loss of employment, physical illness, and financial and legal difficulties may all act as stressors precipitating suicidal behavior in those with a diathesis, or predisposition. Interpersonal events and/or acute life stressors have been associated with suicide in psychological autopsy studies comparing suicides to surviving suicide attempters (201–206). In case–control psychological autopsy studies, the prevalence of "adversity" in the 3 months prior to suicide attempt was 29–93% in suicides compared to 5–88% of nonfatal suicide attempts (86). The type of stressful life event may be important. In both alcohol and psychoactive substance use disorders, loss of close interpersonal relationships was noted within the 6-week period preceding suicide (207, 208). For adolescents and children, psychosocial factors including parent–child conflict, adverse life events, personal relationships, and family history of depression and substance abuse appear to play an important role, comparable to that of psychiatric illness (52). For women in regions where very lethal methods are used such as China, impulsive attempts in the context of social crises and no Axis I disorders are more likely to end up as suicides and probably explain why more females suicide in China than males (88).

Other psychosocial risk factors that have been associated with suicidal behavior include living alone or being socially isolated and unemployment. Population level studies find the unemployed, both males and females, at greater risk for suicide mortality than the employed (209). However, many studies did not consider the presence of a psychiatric disorder, which often contributes to the probability of employment difficulties as well as being a risk factor for suicidal behavior and thus may mediate the relationship between suicide and unemployment. Living alone or being socially isolated is a risk factor for suicide (210) particularly for older adults (145, 211).

33.4.3.7. Availability of Lethal Means

The ready availability of lethal means for suicide increases the likelihood that a suicide attempt will succeed. In 2007, in the United States, 56% of male and 30% of female suicides used firearms (5). Among males 65 years and older, 79.5% of all suicides used firearms (5). In a psychological autopsy of adolescent suicides, the presence of a firearm in the house was a significant risk factor for suicide (212). A recent study of household firearm ownership rates and suicide rates in the United States from 1981 to 2002 found that for every 10% decline in the percentage of households with firearms, there was a decline of 4.2% in overall firearm suicides and a drop of 8.3% in firearm suicides in 0–19 years' age group (213). In Switzerland, where firearms have been prevalent due to a citizen army, reduction of the size of the army by 50% and restricting access to guns after discharge from military reduced the suicide rate by gunshot in army-age men with little evidence of method substitution (214). In other countries, such as Sri Lanka and China, the ready availability of toxic pesticides also means that more impulsive suicide attempts are more often fatal (215). Where a method is commonly used, restriction of that method can reduce national suicide rates, for example, the replacement of coal gas by natural gas and gun control. However, such reductions in national suicide rates may, in part, be offset over time by substitute methods. More limited benefits in terms of reducing suicides have been seen for method restrictions such as using blister packs for sedative medications, erecting barriers on certain bridges popularized as a place to suicide, and the introduction of more effective catalytic convertors in cars.

33.4.4. Protective Factors - Reasons for Living

While the preponderance of suicide research focused on identifying risk factors, there is an emerging interest in protective factors. Higher scores on the Reasons for Living Index can distinguish suicide attempters from non-attempters (216, 217). Religious beliefs, moral objections to suicide, survival and coping beliefs, and family responsibilities also appear to have protective effects against suicidal behavior (218–220).

33.5. Prevention and Treatment

In formulating a management strategy for suicidal patients, three principal aspects require attention: (1) diagnosis and treatment of existing psychiatric disorders, (2) assessment of suicide risk and removal of the means for suicide, and (3) specific treatment strategies to reduce the diathesis or propensity to attempt suicide (see Hirschfeld (221) and Mann (222) for reviews).

33.5.1. Recognizing and Treating Psychiatric Disorders

Failure to diagnose psychiatric illness leaves patients untreated and vulnerable to suicide (223). Most suicides occur in the context of an untreated psychiatric illness. A diagnosis of major depressive disorder, of alcohol/substance use disorder, or of schizophrenia already places the patient at a manyfold increased risk. Comorbidity of alcoholism or substance use disorder also increases the risk of suicide in mood disorders and schizophrenia. Detecting the presence of these disorders and instituting appropriate management and treatment can diminish suicide risk.

About two thirds of suicides have had contact with a primary care physician within a month of death (224, 225), and this high level of medical contact increases the opportunity for effective treatment intervention. Depression and other psychiatric disorders are under-recognized and undertreated in the primary care setting (226, 227), and fewer than one in six patients who commit suicide in the course of a major depressive episode were receiving adequate antidepressant treatment (228). Thus, improving the recognition and treatment of psychiatric disorder in primary care is an important avenue for preventing suicide. Studies examining suicidal behavior in response to primary care physician education programs that target the recognition and treatment of depression in specific locales in Sweden, Hungary, Japan, and Germany have reported increased prescription of antidepressants and/or and declines in suicide rates (229–232) and represent the most striking known example of a therapeutic intervention lowering suicide rates.

In terms of specific pharmacologic treatment of suicidality, there is some evidence of an anti-suicidal effect for lithium in major mood disorders (233) and clozapine in schizophrenia (234, 235). While ecological studies of suicide rates and antidepressant prescriptions rates show declines in suicide rates to correlate with increases in antidepressant prescription rates in adults and youth in Hungary (229), Sweden (236), Australia (237), and the United States (238, 239), meta-analyses of clinical trials of antidepressants have generally not detected benefit for suicide or suicide attempts in mood and other psychiatric disorders (240–242). This may be due to methodological issues such as the low base rate of suicidal behavior and insufficient systematic screening for suicidal behavior, or high-risk individuals may be excluded from trials. More recently, Gibbons et al. showed that

TABLE 33.1. Factors for the assessment of suicidal risk.

Predisposing risk factors	Current risk factors
Previous suicide attempt	Current suicidal ideation—with plan
Family history of suicidal behavior	Episode of major depression
Trait aggression and/or impulsivity	Recent discharge from hospital
Comorbid Cluster B personality disorder	Current alcohol/substance use
Head injury	Current stressful life events
Smoking	Available method
Male, white, living alone	

use of fluoxetine in the clinical trials was associated with a decrease in suicidal ideation that was proportional to the decrease in depression severity in adults, but not children and adolescents (243). Further studies are required in high-risk populations to ascertain if there are specific anti-suicidal properties in antidepressants.

There has been much debate about the possibility of increasing the risk of suicidal behavior with the use of selective serotonin reuptake inhibitors (SSRIs), particularly in children and adolescents, prompting regulatory agencies in the United States, United Kingdom, and Europe to issue warnings. Meta-analysis of US FDA pediatric antidepressant trials initially found that there were small increases in the risk of adverse event reports of suicidal thinking or suicide attempts in youth taking SSRIs and other new-generation antidepressant drugs (244). However, analysis of systematic questionnaire data does not identify an increase in risk for suicidal ideation on SSRIs, raising questions about ascertainment artifacts in the adverse event report method (see Mann et al. (245) for a detailed discussion of this issue). Other lines of evidence including epidemiology, autopsy studies, and cohort surveys do not support the hypothesis that SSRIs induce suicidal acts and suicide in youth (246, 247). Rather they indicate that a negligible number of youth suicides are taking antidepressants at the time of death (248). Clearly young depressed people being treated with SSRIs must be monitored closely for the emergence or worsening of suicidal thoughts, however, concerns must be balanced against the risk of untreated depression in youth as suicide is the third leading cause of death in youth, and over 90% of suicides in depressed youth are untreated at the time of death (248).

33.5.2. Assessment of Suicide Risk

Assessing suicide risk involves evaluating both current suicidal thoughts and plans and acute stressors as well as determining the presence of enduring risk factors that make an individual more likely to act on suicidal feelings. Ascertaining the level of risk for a patient will determine what management strategies to employ. Table 33.1 shows risk factors to evaluate when assessing suicide risk.

33.5.2.1. Enduring Risk Factors

A history of suicidal behavior is a strong indicator that an individual has a propensity to act on suicidal feelings, and detailed inquiries should be made about the timing, lethality, method, intent, and precipitating events of prior suicidal behavior. Since suicidal behavior and the diathesis for suicidal behavior is familial, it is also important to ask about a family history of suicide or nonfatal suicidal behavior. Direct inquiries into past instances of aggressive or impulsive behaviors as well as noting the presence of other known risk factors such as head injury and smoking can contribute to developing an estimation of an individual's likelihood of acting on current suicidal thoughts. Broader demographic risk factors cannot inform much about imminent risk but can add to the overall picture of risk particularly if a patient has several of these risk factors, i.e., an older Caucasian male living alone.

33.5.2.2. Current Risk Factors

Suicidal ideation that includes a plan for suicide, an expression of suicide intent, and evidence of active preparation for a suicide attempt are three indicators of greater short-term risk. Detecting suicidal ideation may necessitate active inquiry on part of clinicians, particularly among male patients who are half as likely as females to report suicidal ideation to their doctor prior to suicide (249). Additional information might be sought from available relatives regarding behaviors indicating planning for a suicide attempt or statements they may have heard from the patient suggesting they have formulated a specific plan or intent to attempt suicide.

Comprehensive assessment of psychiatric condition, particularly major depression including anxiety, insomnia, agitation symptoms, and feelings of hopelessness, is crucial. Treatment history of depression is also important to consider, as suicide risk is increased in the period immediately following discharge from hospitalization (250). Current alcohol and substance use should also be assessed, as well as inquiring into current life events and stressors.

33.5.3. Management

Although there are some published guidelines on the management of suicidal patients available (251), determining the type and level of intervention depends largely on clinical judgment. Overtreatment is preferable to undertreatment, given the serious consequences of a missed suicide attempt, although unwarranted hospitalization is burdensome on both the patient and health-care resources.

For patients deemed to be at imminent risk, such as those expressing severe suicidal ideation defined as a definite plan and strong intent, and having ready access to lethal means, hospitalization should be considered. For individuals at higher, but not imminent, risk, increased vigilance is necessary including more frequent visits and/or telephone contact, helping the patient with a safety plan to help them cope with suicidal thoughts and better gauge when to call for help and where possible enlisting the assistance of a family member or other close friend. Availability of lethal means such as firearms and lethal medications should be determined and their removal arranged. Vigorous treatment of psychiatric disorder should be instituted, including considering ECT for patients with treatment-resistant or psychotic depressions and treatment for alcohol/substance disorder if present. Promising results with ketamine in terms of rapid antidepressant response and amelioration of suicidal ideation need further research but are a potential future option.

Because traits contribute to the diathesis that determines suicidality risk, longer-term treatments need to be considered such as psychotherapies including cognitive behavioral therapy to improve problem solving, reduce hopelessness, and develop better coping strategies for stressful life events. Strengthening protective factors such as psychosocial support systems for suicidal individuals can also increase resilience.

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34
Clinical Psychopharmacology

Matthew A. Fuller, Pharm.D., BCPS, BCPP, FASHP*

Abstract The somatic treatment chapter consists of five narrative sections that include the pharmacotherapeutic agents indicated in the treatment of schizophrenia, depression, mania, all five anxiety disorders, and dementia. An additional section summarizes the hypnotic agents currently available for the treatment of short-term and long-term insomnia. Drug dosing tables congruent with the narrative sections have been inserted.

Each section is organized in a similar fashion with subsections for indications, efficacy, dosing, and adverse effects. The chapter is copiously referenced with primarily randomized controlled trials serving as the basis for the treatment recommendations. The intent of the chapter is to present a succinct summary of a spectrum of clinical psychopharmacotherapeutic data that is sufficiently referenced that the reader is able to consult the primary literature should additional questions arise regarding the recommendations contained in the chapter.

Keywords Psychopharmacology • Schizophrenia • Bipolar disorder • Major depression • Anxiety disorders • Dementias • Sleep medications

34.1. Schizophrenia and Other Psychoses

The chemical antipsychotic classes (e.g., phenothiazine, butyrophenone, thioxanthene, dihydroindolone, and dibenzoxazepine) introduced in the U.S. between 1954 and 1984 are often referred to as "typical antipsychotics." A second generation of antipsychotics has been characterized as "atypical." These drugs include clozapine, risperidone, olanzapine, quetiapine, ziprasidone, aripiprazole, paliperidone, iloperidone, asenapine, and lurasidone. The "atypicality" criterion for antipsychotics is generally regarded as the lesser risk of extrapyramidal adverse effects including tardive dyskinesia. Although the terms "typical" and "atypical" still appear in the medical literature, the use of the terms first-generation antipsychotic (FGA) and second-generation antipsychotic (SGA) are now commonly applied to these agents. The FGA and SGA are primarily used for the treatment of schizophrenia, schizoaffective disorder, bipolar disorder, manic and depressive phases, and as an adjunctive treatment in major depressive disorder (1, 2).

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M.A. Fuller, Pharm.D., BCPS, BCPP, FASHP (✉)
Clinical Pharmacy Specialist, Department of Psychiatry, Louis Stokes Cleveland Department of Veterans Affairs Medical Center, Cleveland, OH, USA
Associate Clinical Professor, Department of Psychiatry, Clinical Instructor, Department of Psychology, Case Western Reserve University, Cleveland, OH, USA
Adjunct Associate Professor of Clinical Pharmacy, University of Toledo, Toledo, OH, USA
e-mail: matthew.fuller@va.gov

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34.1.1. Antipsychotics: Efficacy

34.1.1.1. Schizophrenia

As a treatment for patients diagnosed with schizophrenia, FGA improvement rates range from 40–75%. All FGA are equally efficacious (3). Most treatment guidelines recommend SGA as first-line treatment for schizophrenia versus FGA because of their debatable safer adverse drug reaction (ADR) profile and their small efficacy differences (5). Indeed, results of clinical trials have shown minimal differences in efficacy while adverse effect profile varies with the antipsychotic utilized (522, 523).

The major therapeutic effect of antipsychotics is to ameliorate psychotic symptoms such as the positive symptoms of delusions and hallucinations. Antipsychotics reduce, but rarely eliminate, these symptoms. Early studies reported that "negative symptoms" (e.g., emotional and social withdrawal, poverty of thought, flat affect, ambivalence, poor self-care) usually do not respond as well as positive symptoms to FGA. However, other investigations have indicated equal improvement between positive and negative symptoms (6). Individual studies and meta-analyses indicate that SGA generally, but not always show superiority in improving negative symptoms (1, 4, 7). Like positive symptoms, negative symptoms are rarely fully eradicated. Historically, FGA have been reported to have minimal effect on cognitive disturbances, while SGA are associated with modest improvements (8). However, high doses of FGA leading to ADR and concomitant anticholinergic treatment may have had a negative effect on cognition. A recent study of olanzapine and low-dose haloperidol showed a significant improvement in cognitive function with both drugs (8).

Attempts to predict a response to a specific antipsychotic or to predict a response based on a patient's demographics, psychiatric history, or clinical characteristics have not been successful (9). Literature reports that improvement occurs within several hours or days after initiation of the antipsychotic, with the greatest degree of improvement occurring within 4–6 weeks (10). Recent literature had challenged the notion that antipsychotics have a delayed onset of action. Agid and colleagues suggest that more antipsychotic improvement is seen within the first two weeks than in any other two week period thereafter (524–526). It is recommended that patients receive an adequately dosed antipsychotic trial of at least four weeks before considering a change in treatment. Being the drug of "last resort", the trial period for clozapine is at least three months. Long-term studies indicate that the maximum therapeutic benefit with FGA and SGA excluding clozapine may take up to 3–6 months (11). If a patient does not respond to an adequate trial of an antipsychotic of one chemical class, a drug in another class may be tried (12).

The first acute episode of schizophrenia requires continuous antipsychotic treatment for a minimum of 12 months. The relapse rate risk ranges from 60%–90% over the next 2–3 years if the FGA is discontinued (13). Although the relapse risk is high, patients may be given a trial off antipsychotics after a 1–2 year period without symptoms to determine whether there is a continuing need for medication (14).

34.1.2. Second Generation Antipsychotics

34.1.2.1. Efficacy

34.1.2.1.1. Schizophrenia

A meta-analysis of FGA and SGA across 10 studies indicated that clozapine, risperidone, and olanzapine produced greater improvement than FGA. Quetiapine, ziprasidone, and aripiprazole did not differ from the FGA (1). Clozapine, risperidone, and olanzapine were slightly superior on positive symptoms, but moderately superior on negative, cognitive, mood and impulse control symptoms as compared to the FGA (15). A meta-analysis of SGA head-to-head comparison studies reported no differences between olanzapine versus risperidone, ziprasidone versus olanzapine and aripiprazole versus risperidone. Thus the choice of a SGA is based primarily on differences within ADR profile and cost rather than efficacy. The National Institute of Mental Health-sponsored CATIE trial results demonstrated no significant differences in efficacy rating scales scores between the SGA olanzapine, quetiapine, risperidone, or ziprasidone, and the FGA perphenazine. Sixty-four percent of olanzapine-treated patients discontinued the medication before the completion of the 18-month study, which was significantly less than for the four other agents thereby suggesting greater effectiveness. Overall, 74% of patients discontinued antipsychotic treatment for all causes. Olanzapine was discontinued significantly more often (9%) due to metabolic symptoms (glucose, lipid) or weight gain. Perphenazine was discontinued in 22% of patients due to extrapyramidal side effects (16).

Clozapine's efficacy has been compared with multiple FGA. In 8 of the 12 studies, clozapine was more effective than the reference antipsychotic, three studies demonstrated equal efficacy, and one found clozapine to be less effective. Clozapine, due to its hematological ADR profile, can only be used in patients refractory to or not tolerating two or more antipsychotic trials (17). The SGA have not been studied as frequently as the FGA in maintenance treatment of patients. Controlled studies suggest they are effective. More studies for longer durations need to be conducted.

34.1.2.1.2. Refractory Schizophrenia

Multiple studies have shown that patients who do not respond to FGA may respond to an SGA (18). If patients have failed two sequential trials of an SGA excluding clozapine, FGA, or an SGA and FGA, the clinician should consider clozapine for the patient. Patients should not be considered refractory to treatment until they have had a trial of clozapine (1, 15). Clozapine with few exceptions is proven more effective than the FGA and other SGA in the treatment of refractory patients, if adequate serum levels or doses are utilized (1, 15). However, since many studies have not utilized serum levels to determine the effective dose, the efficacy of clozapine versus all other antipsychotics is probably an underestimate (1).

Because of its potential adverse hematologic effects, the Food and Drug Administration (FDA) has restricted clozapine to patients who are refractory to typical antipsychotics or to those with severe intolerable ADR. Clozapine is also FDA-indicated for the reduction of risk of recurrent suicidality in patients with schizophrenia or schizoaffective disorder (19).

Of drugs available in the US, clozapine has been compared with several FGA. In acutely psychotic or chronically ill patients with schizophrenia, clozapine was equal to or more effective than the reference typical. A meta-analysis of studies comparing clozapine and the SGA olanzapine and risperidone found no significant differences (1). A later analysis demonstrated, however, that clozapine was more efficacious than risperidone in the studies where higher doses of clozapine were used (15). The CATIE trial determined that open-label clozapine showed greater effectiveness than another antipsychotic after failure of a first antipsychotic (20). A retrospective study reported that about 40% of patients were able to return to part-time or full-time employment after treatment with clozapine (21). Another retrospective report on 87 treatment-resistant patients indicated that clozapine provided an average savings of $9000–14000 in "mental health services" after 2 years of treatment (22). Clozapine studies indicate that negative symptoms respond as well as positive symptoms (23).

34.1.2.2. Concomitant Antipsychotic Prescribing

The use of two or more SGA concomitantly is not currently supported by published literature. At this time, the only combination studies published include controlled investigations of risperidone added to clozapine; the first trial found statistically significant improvement in symptoms, but the difference was of questionable clinical significance (24). The second and third studies reported no benefit for the combination (25, 527). The use of combinations may also lead to additional ADR burden, as well as dramatically increasing the cost of treatment. Therefore, the use of SGA in combination is not recommended unless the patient has failed a trial of each individual drug as well as clozapine or clinical judgment and symptomatic improvement in a patient warrants their co-administration.

34.1.2.3. Schizoaffective Disorder

It is difficult to assess the overall efficacy of antipsychotics for schizoaffective disorder. SGA, with the exception of clozapine, are utilized in combination with the primary treatment, lithium, when psychotic symptoms are prominent (1). Many studies combine patients with diagnoses of schizophrenia, schizoaffective disorder, or schizophreniform disorder when reporting outcomes, making it difficult to assess the response or relative efficacy for these agents. Clozapine has been reported to be moderately effective in 50% to 70% of patients, but only in non-blind reports (26).

34.1.2.4. Mania

All SGA with the exception of clozapine, iloperidone, lurasidone, and paliperidone are approved by the FDA for the treatment of acute mania (528–530). Clozapine has been reported effective for mania in uncontrolled studies and retrospective reports (26). Controlled trials have reported onset of action of 2–7 days for risperidone, olanzapine, ziprasidone, and aripiprazole, and 21 days for quetiapine (28). Most studies that have compared lithium and SGA for treating patients diagnosed with acute mania have not utilized therapeutic lithium levels, and that treatment response for most of those studies has been considered greater than 50% symptom reduction and not complete resolution. Major treatment guidelines for bipolar disorder conclude that primary mood stabilizers are first-line treatment for acute mania. However, current guidelines need to be updated (29). If an SGA is combined with a primary mood stabilizer, it should be discontinued once complete resolution of symptoms has occurred.

Olanzapine, aripiprazole, risperidone, quetiapine, and ziprasidone are the SGA approved for maintenance or prophylactic, treatment of bipolar illness. Their efficacy as compared with proven treatments such as lithium is not well established, since most data compare these agents only to placebo (27, 29). However, they may be utilized as first-line options along with primary mood stabilizers for the maintenance treatment of bipolar disorder.

34.1.2.5. Cognitive Disorders

Psychotic symptoms among patients with cognitive disorders can lead to behavioral disturbances during which they become hostile, agitated, aggressive, and dangerous to themselves and others (30). Patients may become agitated, hostile, aggressive, and dangerous to themselves or their surroundings (30). The efficacy of SGA have been investigated in seven controlled trials, including two with risperidone, four with olanzapine, and one with quetiapine, for the treatment of psychosis and behavioral disturbance in Alzheimer's disease (31). The studies generally reported SGA were better than placebo. It is important to note that the clinical response is generally restricted to minor to moderate reduction in hallucinations, delusions, agitation, and aggression. Risperidone, haloperidol, and quetiapine have been contrasted in studies investigating the efficacy of these agents in treating aggression. Risperidone was superior to, and quetiapine was equal to haloperidol (31). In 2005, a black box warning was issued for all SGA, because the mortality rate from cardiovascular and infectious (pneumonia) events among geriatric patients diagnosed with dementia was twofold higher than the placebo group in 10-week studies. In a study comparing olanzapine, quetiapine, risperidone or placebo in patients with Alzheimer's disease, improvements were seen in anger, aggression and paranoid ideas. Improvement in functioning, care needs, and quality of life was not found (531). Further analysis revealed that atypical antipsychotics were associated with worsening of cognitive function (532). A benefit to risk assessment should be undertaken prior to utilizing antipsychotics in patients with dementia.

34.1.2.6. Dosing: Second-Generation Antipsychotics (SGA)

Current recommendations for changing from one antipsychotic to another include a cross-taper, where current medication would be tapered for four weeks while the dose of the new medication is increased. Although not extensively researched, this conservative practice is theorized to reduce the risk of patient relapse.

34.1.2.6.1. Aripiprazole

The recommended initial and target dosages of aripiprazole when used for the treatment of schizophrenia are 10 to 15 mg/day. The maximum FDA-approved dose is 30 mg/day. Efficacy has not been found to be significantly greater with higher doses (32). When used in the treatment of acute mania, the initial dose of aripiprazole in some clinical trials was up to 30 mg once daily (33). Approximately 15% of the study population in those trials required a decrease in dose to 15 mg daily based on tolerability. The safety of doses greater than 30 mg daily has not been determined. Doses may be given once daily without regard to meals. Dose adjustments should be made at no faster than two-week increments (33).

The efficacy of intramuscular aripiprazole for injection for the treatment of agitation was established in three short-term (24-hour), placebo-controlled trials in agitated inpatients with either schizophrenia or bipolar I disorder. Agitation associated with schizophrenia or bipolar mania may be treated with intramuscular aripiprazole. The initial dose is 9.75 mg and the maximum dose is 30 mg/day (533).

The recommended starting and maintenance dose of aripiprazole long-acting injection (LAI) is 400 mg monthly. Oral therapy should overlap the injection for 14 days. Patients who are CYP2D6 poor metabolizers and patients taking CYP2D6 (fluoxetine, paroxetine) or CYP3A4 (clarithromycin, ketoconazole, ritonavir) inhibitors should receive 200–300 mg. Those patients receiving a CYP2D6 and CYP3A4 inhibitor should receive 160–200 mg. It is recommended that aripiprazole LAI be avoided in patients receiving CYP3A4 inducers (carbamazepine, phenobarbital, phenytoin, rifampin). The long-acting intramuscular injection should be administered in the gluteal muscle (534).

In addition to the intramuscular dosage forms, aripiprazole is available as an oral disintegrating tablet (ODT) and oral solution. The ODT dosage form dissolves rapidly in saliva and may be swallowed without liquid. The oral solution may be interchanged with tablets on a milligram per milligram basis up to 25 mg. Doses using 30 mg tablets should be exchanged for 25 mg of oral solution.

Aripiprazole is indicated for the treatment of schizophrenia, bipolar disorder, as an adjunctive treatment of major depression, irritability associated with autistic disorder, and agitation associated with schizophrenia or bipolar disorder (533).

34.1.2.6.2. Asenapine

The recommended initial and target dosage of asenapine when used for the treatment of schizophrenia is 5 mg twice daily. The maximum FDA approved dose is 10 mg twice daily. The initial and target dosage of asenapine when used as monotherapy in bipolar mania is 10 mg twice daily. When utilized as an adjunct to lithium or valproate in bipolar mania the initial and target dose is 5 mg twice daily. The maximum dosage is 10 mg twice daily. Asenapine is a sublingual tablet that should be placed under the tongue and left to dissolve completely. It should not be swallowed. Eating and drinking should be avoided for 10 minutes after administration (535).

Common side effects associated with asenapine include: akathisia, oral hypoesthesia, somnolence and extrapyramidal symptoms.

34.1.2.6.3. Clozapine

The recommended initial dose for patients with refractory schizophrenia or schizoaffective disorder is 12.5 mg once or twice daily. Doses may be increased by 12.5–50 mg/day, if tolerated. The usual target dose range is 300–450 mg/day, administered either twice daily (BID) or three times daily (TID). A serum clozapine level should be obtained after the target dose is reached and steady state is achieved. Further dose increases may be titrated on a once-or twice-weekly basis in increments of 50 or 100 mg/day, if necessary. The maximum recommended daily dose of clozapine is 900 mg/day, but measurement of clozapine levels are advised as a guide for potential dose adjustments and daily dose. Clozapine serum levels should be obtained 12 hours after the last dose. Published literature indicates that higher response rates were achieved in patients with threshold levels exceeding 500 ng/ml (34). If greater than 48 hours of doses are missed, the patient should be re-titrated with the recommended starting doses to minimize the risk of syncope. Based on the patient's previous ADR, the patient may undergo a more rapid re-titration (35).

34.1.2.6.4. Iloperidone

The recommended initial dosage for iloperidone for the treatment of schizophrenia is 1 mg twice daily. Adjustments may be made daily to 2 mg, 4 mg, 6 mg, 8 mg, 10 mg and 12 mg twice daily on days 2, 3, 4, 5, 6, and 7 respectively. The target dosage for iloperidone for the treatment of schizophrenia is 12 to 24 mg/day administered twice daily. The initial daily titration is recommended to minimize the potential for orthostatic hypotension. Iloperidone can be administered without regard to meals (528).

Common side effects include: dizziness, dry mouth, fatigue, nasal congestion, orthostatic hypotension, somnolence, tachycardia, and weight gain.

34.1.2.6.5. Lurasidone

The recommended stating dose of lurasidone for the management of schizophrenia is 40 mg once daily. The maximum recommended dose is 160 mg once daily. Lurasidone should be taken with food.

Lurasidone's dosage should be adjusted in patients with moderate and severe hepatic and renal impairment as well as when used concomitantly with moderate inhibitors of CYP3A4 (diltiazem). In patients with moderate and severe renal impairment the recommended starting dose is 20 mg daily and the maximum recommended dose is 80 mg daily. When utilized in patients with moderate and severe hepatic impairment the recommended starting dose is 20 mg daily. The maximum recommended dose is 80 mg daily in moderate hepatic impairment and 40 mg daily in patients with severe hepatic impairment. The recommended starting dose is 20 mg and the maximum recommended dose is 80 mg daily when used concomitantly with moderate inhibitors of CYP3A4 (529).

Common side effects include: akathisia, extrapyramidal symptoms, nausea, and somnolence.

34.1.2.6.6. Olanzapine

Initial doses for patients with schizophrenia are 5 to 10 mg/day, given as a single daily dose (36). A target dose of 10 mg/day may be reached within several days of initiation. Dosage adjustments should be made at intervals of not less than one week, and decreases or increases may be changed by 5 mg/day. The maximum FDA-approved dosage is 20 mg/day. Effective doses in clinical trials have ranged from 10 to 15 mg/day (36). Doses from 7.5 to 40 mg/day have been reported effective in patients with schizophrenia (37). Doses may be given once daily, without regard to meals. Due to the potential ADR of sedation, the dose is commonly given at bedtime. Clinical trials for the short-term treatment of acute mania showed efficacy with 5–20 mg/day; the recommended initial dose is 10 or 15 mg/day. In clinical trials evaluating the short-term (3 to 4 weeks) effects of olanzapine in acute mania, efficacy was observed with doses of 5 to 20 mg/day (36). Doses above 20 mg/day have not been evaluated for safety in clinical trials. The recommended initial dosage of olanzapine in combination with lithium or valproate is 10 mg once daily (36). Bipolar patients responding to initial olanzapine therapy for an average period of two weeks have been successfully maintained on olanzapine monotherapy at a dose of 5 to 20 mg/day. Short-acting intramuscular olanzapine for injection is intended for intramuscular use only. The efficacy of intramuscular olanzapine for the treatment of agitation associated with schizophrenia or mania has been shown at doses from 2.5 to 10 mg (36). Although the efficacy of repeated doses of IM olanzapine has not been evaluated, persisting agitation after initial doses may be treated by subsequent injections, up to a total of 30 mg. The safety of total daily doses greater than 30 mg given more frequently than 2 hours after initial dosing and 4 hours

after the second dose have not been evaluated. Parenteral benzodiazepines should be avoided with short-acting intramuscular olanzapine due to a risk of cardiorespiratory depression with the combination.

The recommended dosage for long-acting intramuscular olanzapine depends on the patients established dose of oral olanzapine. Those established on 10 mg/day should be given 210 mg every 2 weeks for 4 doses or 405 mg every 4 weeks for 2 doses. The maintenance dose is 150 mg every 2 weeks or 300 mg every 4 weeks. Those established on 15 mg/day should receive 300 mg every 2 weeks for 4 doses with a maintenance dose of 210 mg every 2 weeks or 405 mg every 4 weeks. Patients established on 20 mg/day should receive an initial and maintenance dose of 300 mg every 2 weeks (536).

34.1.2.6.7. Paliperidone

The recommended dose of paliperidone for the treatment of adults with schizophrenia or schizoaffective disorder is 6 mg once daily. The recommended range is 3–12 mg daily. The maximum recommended dose is 12 mg/day. Dose increases above the initial 6 mg/day dosages should be made at intervals of more than 4–5 days. When dose increases are indicated, increments of 3 mg/day are recommended.

The recommended starting dose of paliperidone for the treatment of schizophrenia in adolescents 12–17 years of age is 3 mg once daily. Dose increases should be made at intervals of more than 5 days in increments of 3 mg/day.

Paliperidone can be taken with or without food (530)

Common side effects include: akathisia, extrapyramidal symptoms, tachycardia, and somnolence.

34.1.2.6.8. Risperidone

The recommended titration schedule for risperidone used in the treatment of schizophrenia is 1 mg twice daily for one day, 2 mg twice daily for one day, and 3 mg twice daily thereafter. Further dose changes should be no faster than increments of 1 mg per week. Patients not responding to treatment after 4 weeks may be considered for doses higher than 6 mg day if they have not experienced EPS. The optimal dose of risperidone in dose-response studies has been shown to be 6–8 mg daily (37). The recommended starting dose of risperidone long-acting injection (Risperdal Consta) for the treatment of symptoms of schizophrenia is 25 mg IM every two weeks. Clinical effects from dosage adjustments (including initial dosing) should not be expected earlier than three weeks following the first injection of the dose, and dosage increments should not be attempted more frequently than every 8 weeks. The maximum approved dose is 50 mg every two weeks. Doses should be given every two weeks. Prior to starting treatment, all patients should be tested for tolerability to risperidone if they have not previously been treated with the oral formulation. It is important to remember that IM injection should be administered with the safety needle provided in the drug packaging for the health care professional's use. The drug is administered into either the deltoid muscle or the upper outer quadrant of the gluteal area. Injections should be alternated between the two buttocks (38). Oral risperidone should be given with the initial injection of risperidone long-acting injection and continued for at least 3 weeks after which it may be discontinued. The prescribing information indicates that when using oral risperidone for acute mania, doses should be started at 2 to 3 mg given as one daily dose. Dosages should not be adjusted more than every 24 hours and or exceed 1 mg increments. Dosages exceeding 6 mg daily were not studied in the clinical trials for acute mania (39).

34.1.2.6.9. Quetiapine

The recommended starting dose for quetiapine used to treat symptoms of schizophrenia is 25 mg twice daily. On the second or third day, the dosage may be increased in increments of 25 to 50 mg two or three times a day. A target dose of 300 to 400 mg daily, divided in 2 or 3 doses, may be reached by the fourth day. The average dose in clinical trials ranged from 300 and 400 mg daily as two or 3 divided doses, although efficacy has been demonstrated in the dose range of 150 to 750 mg daily. The usual dosage range is 300–800 mg/day. The efficacy of doses greater than 800 mg daily has not been systematically studied. The recommended initial dose of quetiapine when used to treat symptoms of acute bipolar mania is 100 mg daily in two divided doses, increased to 400 mg by day 4 in increments of up to 100 mg daily in two divided doses. Subsequent dosage adjustments may be done in increments of no more than 200 mg daily, up to a maximum of 800 mg daily by day 6, if necessary. When patients have not taken quetiapine for greater than one week, the medication must be re-titrated; however, if the patient has missed less than one week, titration of dose is not required (40).

The recommended dose of quetiapine for the treatment of bipolar depression is 50 mg daily on day one; increasing to 100 mg daily on day two. Further increasing by 100 mg/day each day until a target dose of 300 mg once daily is reached by day four. The maximum recommended dose is 600 mg daily (537).

34.1.2.6.10. Ziprasidone

Initial dosing, when used to treat the symptoms of schizophrenia, is 20 mg twice daily with food. Dose adjustments, if necessary, should occur at intervals of at least 2 days. Daily dosage may be adjusted up to 80 mg twice daily. The safety of dosages above 200 mg daily has not been studied, and justification and electrocardiographic (ECG) monitoring is recommended to be documented on the patient record if the patient's dose exceeds 160 mg/day. It is recommended that patients should be monitored for treatment response for several weeks prior to upward dosage titrations. The recommended initial dose of ziprasidone when used to treat the symptoms of acute mania is 40 mg twice daily with food. The dose may be increased to 60 or 80 mg twice daily on the second day of treatment. Further dosage adjustments should be made in regards to tolerability and efficacy (41). Ziprasidone injection for intramuscular administration may be used for patients with schizophrenia experiencing symptoms of acute agitation. The recommended dose is 10 to 20 mg per injection, to a maximum daily dose of 40 mg (41). The administration of intramuscular ziprasidone has not been studied in excess of 3 days.

34.1.2.7. Adverse Effects

The section below discusses adverse drug reactions (ADR) of the SGA. Specific information about certain agents is included within the summaries.

34.1.2.7.1. Autonomic

Autonomic nervous system ADR of the SGA are products of adrenergic blockade, autonomic hyperactivity (antipsychotic withdrawal), and cholinergic blockade (42). Constipation is often considered a dose-related problem. It may disappear with continuation of the same dose, although dose reduction may be considered with significant constipation. Dry mouth is also a dose-related ADR. Up to 80% of clozapine-treated patients will complain of some degree of excessive salivation, especially at night. Nausea and vomiting are dose-related ADR that have occurred after several weeks of clozapine treatment; these ADR may disappear with continuation, but may be treated by dose reduction or temporary discontinuation if the effect does not subside (5). Withdrawal reactions have been reported with clozapine upon abrupt cessation of the medication, including diaphoresis, confusion, agitation, restlessness, headache, nausea, vomiting, or diarrhea. These effects are postulated to occur because of cholinergic rebound.

While anticholinergic side effect are common with clozapine, they are less common with olanzapine and quetiapine and uncommon with asenapine, aripiprazole, iloperidone, lurasidone, risperidone, paliperidone, and ziprasidone.

34.1.2.7.2. Cardiovascular

Hypotension/dizziness are observed with clozapine during the initiation of treatment and/or after dose escalation at an estimated incidence of up to 13%. Asenapine, iloperidone, risperidone, paliperidone, olanzapine, and quetiapine have also been reported to cause dizziness and orthostasis (36, 39, 40, 528); however, lurasidone, ziprasidone and aripiprazole have not been commonly associated with orthostatic hypotension. Hypertension has been reported in 4% of clozapine-treated patients undergoing rapid dose titrations; tolerance usually develops to this effect. Olanzapine 10 mg/day produced an increase of 3.6 mm Hg in standing systolic blood pressure as compared to placebo, a statistically but not clinically significant finding (43). Tachycardia is a dose-related effect of clozapine that occurs frequently in patients and may approach 120 beats/min. Quetiapine, paliperidone, and iloperidone are also associated with tachycardia. Syncope is infrequently experienced with clozapine (35). Cardiomyopathy has been reported in clozapine-treated patients, with similar reporting rates as estimated in the US general population (35). If cardiomyopathy occurs, clozapine should be discontinued unless the benefit of treatment outweighs the risk. Myocarditis has been reported in 82 clozapine-treated patients in the US, UK, Canada, and Australia, resulting in rates 17 to 322 times higher than rate of myocarditis in the general population. Prompt discontinuation is warranted on suspicion of myocarditis (35).

ECG Changes

ECG changes have been reported with the SGA at varying frequencies. In clinical trials, ziprasidone was found to increase the QTc interval 9–14 msec more than with risperidone, olanzapine, quetiapine, and haloperidol, but 14 msec less than with thioridazine. There has been no indication in post-marketing surveillance that ziprasidone's effect on QTc progresses to torsades de pointes or death. A baseline ECG is recommended before ziprasidone initiation; if QTc exceeds 500 ms, ziprasidone is contraindicated. Ziprasidone should be used with caution if QTc is between 440 ms and 500 ms. Patients at risk for electrolyte disturbances should have baseline serum potassium and magnesium measured. Reversible, nonspecific ST-T wave changes, T-wave

flattening, or inversions have been reported with clozapine infrequently. These dose–related changes are similar to the FGA (44). Iloperidone may increase QTc interval and this effect is augmented when used in combination with CYP2D6 (fluoxetine, paroxetine) and CYP3A4 inhibitors (clarithromycin, ketoconazole, ritonavir). It is recommended that iloperidone be avoided in combination with other drugs known to prolong QTc interval (528, 530, 535). It is also recommended that quetiapine, paliperidone and asenapine be avoided in combination with other drugs that are known to cause QTc prolongation (530, 535, 537). Risperidone was reported to lengthen QTc interval in phase III trials; however, a subsequent review found no evidence that risperidone was associated with torsades de pointes or sudden death (44). Olanzapine has not been associated with significant changes in ECG (44, 45). Aripiprazole has been reported to be associated with QTc interval prolongation only rarely (33). Lurasidone has minimal effects on the QTc interval (529).

Stroke

To date, there have been four large observational studies published examining the risk of cerebrovascular events (CVE) and antipsychotic use (46–49). In none of these observational studies was a significant risk of CVE associated with SGA relative to FGA found. This was also true when the authors compared individual SGA agents relative to FGA, as well as when comparisons were made between individual SGA agents. However in none of the observational studies did the authors stratify by type of dementia, and in only one study did the authors include a non-antipsychotic (benzodiazepine) comparison arm.

34.1.2.7.3. Endocrine

Diabetes

There is a greater than expected rate of obesity in patients with schizophrenia, which might place predisposed patients at greater risk for development of diabetes (51, 52). Clozapine and olanzapine, risperidone and quetiapine are the SGA most commonly indirectly associated with diabetes (51). This is not surprising since these antihistaminic drugs are more likely to cause significant weight gain than ziprasidone, lurasidone and aripiprazole thereby increasing the risk of diabetes. However, the FDA decided in 2004 that, due to a lack of data about all agents, the monitoring for this adverse event should apply equally to all agents (52). Plasma glucose may increase significantly within 8 to 14 weeks of antipsychotic initiation. Monitoring guidelines have been suggested, including fasting plasma glucose or hemoglobin A1c at baseline, 4 months, and annually thereafter (53). Additional routine monitoring parameters recommended by the consensus conference include measurement of body mass index, waist circumference, blood pressure, and fasting lipids (53).

Prolactin

The occurrence of prolactin elevations, which may produce clinically significant sexual, reproductive, endocrine, and mood effects, differs for the individual SGA. Risperidone is associated with dose dependent prolactin elevation especially at doses over 6 mg/day (54). Olanzapine at doses between 20 and 40 mg/day has been associated with increased prolactin levels, but doses 20 mg and less have not (43). Prolactin level increases with ziprasidone are transient, returning to baseline within 12 hours of the dose (55). Prolactin elevations in short term trials in females treated with lurasidone was 5.7% compared to 2% for placebo (529). Short term trial with asenapine revealed elevations in prolactin from 2.3%–2.6% with asenapine versus 0.6%–0.7% with placebo (535). Amenorrhea, galactorrhea, and gynecomastia have not been reported with clozapine but have been reported with paliperidone. Amenorrhea and galactorrhea are reported in 10% of female patients receiving risperidone. Iloperidone may cause gynecomastia and galactorrhea. Olanzapine has been associated with galactorrhea in a case report. Quetiapine, ziprasidone, and aripiprazole have not been reported to cause amenorrhea, gynecomastia, or galactorrhea (56).

Weight Gain

Weight gain is commonly seen in patients with schizophrenia. Antipsychotics may contribute to this weight gain (16, 51). Clozapine has been associated with weight gain. A 7.5 year study reported that 50% of patients gained more than 20% of their pretreatment weight, and most patients gained the majority of their weight during the first year of treatment (57). The propensity to cause weight gain for the other SGA has been mandated by the FDA as the percentage of patients who gain greater than 7% of their baseline body weight during trials lasting 6 to 8 weeks. Olanzapine was greatest at 29% followed in descending order by quetiapine (23%), paliperidone (adolescents 19%), risperidone (18%), iloperidone (18%), ziprasidone (10%), paliperidone (adults 9%) aripiprazole (8%), asenapine (4.9%) and lurasidone (4.8%). The magnitude of the weight gain with olanzapine and other medications is probably dose dependent (58).

Lipid Abnormalities

Clozapine and olanzapine are 4–5 times more likely to be associated with elevations in triglyceride levels, but risperidone has a low risk (2.7%) as does it's metabolite, paliperidone (51, 538). The proportion of patients taking quetiapine was associated

with a 9%–18% increases in cholesterol and a 14%–22% increases in triglycerides (537). The proportion of patients on iloperidone who displayed an increase in cholesterol was 3.6% while 10.1% of these patients had an increase in their triglycerides (528). Lipid abnormalities appear to be minimal with asenapine, lurasidone, ziprasidone and aripiprazole (33, 41, 529, 535).

34.1.2.7.4. Hematologic

Clozapine has been reserved for patients with treatment refractory schizophrenia due to its hematologic ADR profile. Clozapine was removed from the international market in 1975 after reports of deaths related to agranulocytosis were associated with the medication. Clozapine was not marketed in the US until 1990. Early experience in the United States showed an estimated incidence of 0.8% after 1 year of treatment, and 0.91% after 1.5 years. Most cases (84%) occurred within the first three months of treatment. Risk factors include the first three months of treatment, older age, female gender, and a 15% or greater spike in WBC (59, 60). At this time, a baseline and weekly white blood cell count (WBC) with differential is required for the first six months of treatment. During the subsequent 6 months, WBC must be monitored every other week. After that time, WBC must be monitored every four weeks for the duration of treatment. Current guidelines indicate that clozapine should be immediately discontinued if the total WBC falls to <2000 cells/mm^3 or the absolute number of polymorphonuclear leukocytes falls to <1000 cells/mm^3. The patient should not receive clozapine again, as the hematologic reaction might be immune mediated. Re-exposure may result in a rapidly progressive course. The complete blood monitoring guidelines are available on the manufacturers' websites. Eosinophilia has been reported to occur in 1% of clozapine-treated patients. Leukocytosis has been reported in 0.6% of clozapine-treated patients. No routine hematologic monitoring is currently recommended for any other SGA.

34.1.2.7.5. Hepatic

Elevations in serum alanine aminotransferase (ALT) above 200 IU/L were reported in 2% of patients treated with olanzapine. Elevations in aspartate and alanine aminotransferases and gamma-glutamyl transferases were observed in 10% of patients, which appear to be dose dependent (45). It is recommended that liver function be monitored, especially with use of higher doses or longer durations of treatment (45). Transient elevations in serum transaminases, mainly ALT, have been reported with asenapine and quetiapine (40, 535); transaminase elevations of greater than three times normal limits was reported in 6% of patients treated with quetiapine. These elevations occurred within the first three weeks and returned to prestudy levels with ongoing treatment. Ziprasidone has been associated with occasional, clinically insignificant, increases in liver enzymes (61). Mild increases in liver enzymes have been reported with clozapine in routine monitoring, but without significant clinical consequences (42). Aripiprazole, iloperidone, lurasidone, paliperidone, and risperidone are not generally associated with hepatic enzyme elevations (528–530, 533, 538).

34.1.2.7.6. Neuroleptic Malignant Syndrome

Cases of neuroleptic malignant syndrome have been reported with all SGA (62). The incidence is unknown. NMS associated with clozapine is thought to produce fewer extrapyramidal reactions, less muscle rigidity, a milder fever, a smaller increase in creatine phosphokinase, and a higher rate of autonomic dysfunction than NMS reported with FGA. Case reports of NMS presenting similarly to clozapine have been reported with all other SGA.

34.1.2.7.7. Pancreatitis

Risperidone-associated pancreatitis occurred among 16% of 192 patients. Several cases of pancreatitis have been associated with clozapine, and a case has been reported with olanzapine (63).

34.1.2.7.8. Neurologic

Cognition

Neurocognitive impairment occurs in up to 60% of patients with schizophrenia (62). Antipsychotics may improve cognition. However, altered cognition, such as anticholinergic delirium, with SGA may also occur. Clozapine, olanzapine, and risperidone were found to improve verbal learning and executive functioning. Olanzapine and clozapine were found to produce impairment in memory, but risperidone had a minimal effect, perhaps related to its intrinsic lack of anticholinergic effect (62).

While anticholinergic side effect are common with clozapine, they are less common with olanzapine and quetiapine and uncommon with asenapine, aripiprazole, iloperidone, lurasidone, risperidone, paliperidone, ziprasidone. The overall effects of SGA on cognition are inconclusive (557).

Extrapyramidal Side Effects, Early Onset
Overall, the SGA are associated with a decreased risk for acute EPS as compared to the FGA. Short-term administration of clozapine has been associated with tremor and rigidity in up to 3% of patients but dystonia has not been reported. Akathisia has been reported in 0 to 39% of clozapine-treated patients. Since akathisia associated with FGA has been reported to improve with clozapine treatment, more controlled studies, need to be performed to assess this side effect in clozapine-treated patients. Risperidone at 6 mg/day produces fewer EPS than haloperidol 10 to 20 mg/day (64). Incidence and severity of EPS increase as the risperidone dose increases over 6 mg/day. Although EPS have not been commonly reported in patients with schizophrenia, the manufacturer reports rates of 15–32% of patients, presenting most commonly with parkinsonism and akathisia (38). Ziprasidone has been associated with akathisia in 14% of patients, with lower rates of parkinsonian symptoms, dystonia, and hypertonia (41). EPS symptoms have been reported at rates similar to placebo for aripiprazole in adult patients with schizophrenia, although akathisia occurred slightly more frequently (33). However, pediatric patients and patients with affective disorders had much higher rates of EPS (533). Rates of EPS reported at the maximum dose for asenapine, iloperidone and lurasidone are 12%, 15.1%, and 20% respectively (528, 529, 535).

Extrapyramidal Side Effects, Late Onset (Tardive dyskinesia)
Clozapine has not been clearly documented to produce tardive dyskinesia, although three isolated cases have been reported (65). Case reports of tardive dyskinesia associated with risperidone have been reported, but it has been suggested that since risperidone causes less early onset EPS than FGA, that the rate of tardive dyskinesia may be smaller as well (66). Olanzapine and haloperidol comparisons across three studies showed a lower incidence of tardive dyskinesia with olanzapine (67). A study at a movement disorders clinic found 3.4% of patients to have aripiprazole-associated tardive dyskinesia (539). There are little data to report on the development of tardive dyskinesia with iloperidone, asenapine, and lurasidone, as they have been marketed for a relatively short period.

Sedation
Sedation is a dose-related ADR. The rate of sedation differs among the SGA, and is reported to subside with continued treatment or dose reduction. Sedation is most common with clozapine, quetiapine, olanzapine, asenapine, lurasidone and least likely with aripiprazole, risperidone, iloperidone, paliperidone, and ziprasidone.

Seizures
The seizure rate associated with clozapine treatment has been reported to relate to dose and rate of dose increase, although one study failed to find a dose-related association. Seizure risk is reported at a rate of 5% with doses between 600–900 mg daily (5). Between 22% and 74% of clozapine-treated patients may have abnormal electroencephalograms (EEG). Seizures have been reported in less than 1.0% of patients receiving risperidone, olanzapine, quetiapine, ziprasidone, and aripiprazole (39–41, 68).

34.1.2.7.9. Ophthalmologic

Quetiapine has been associated with cataract formation in dogs, so the manufacturer has recommended monitoring by slit-lamp examination.

34.1.2.7.10. Psychiatric

Obsessive-compulsive symptoms have been rarely reported with clozapine, olanzapine, and risperidone. Return of psychotic and negative symptoms within several days of abrupt clozapine or quetiapine discontinuation, or "rebound psychosis" has been described, although some reports question this effect (540). Risperidone has also been reported to be associated with this effect in case reports. A month long cross-taper period is recommended when switching between SGA. Agitation and anxiety were reported in patients receiving risperidone. It is possible that akathisia will have contributed to this finding. Insomnia was found to occur in 54% to 58% of patients receiving risperidone. Insomnia has been reported in 12% of olanzapine and 12% of quetiapine treated patients (36, 40). Iloperidone has rarely been associated with insomnia while lurasidone has been reported to cause insomnia in 10% of patients and asenapine has been associated with insomnia in 6–15% of patients (528, 529, 535).

34.1.2.7.11. Urinary

Enuresis, urinary frequency and urgency, urinary hesitancy, or retention may occur in up to 41% of patients treated with clozapine, which may be an underestimate due to underreporting (39). Cases of enuresis associated with risperidone and olanzapine have also occurred; the manufacturer reports a 2% incidence of enuresis with olanzapine (36).

34.1.2.7.12. Sexual Dysfunction

Anorgasmia, ejaculatory dysfunction, impotence, and decreased libido have all been associated with antipsychotics, including approximately 1% with clozapine. This is probably an underreported issue.

Priapism
Three cases of priapism have been reported with clozapine, and three cases have been reported with risperidone. Cases have been reported with olanzapine, and one case has been reported with quetiapine, as well as one case with ziprasidone.

34.1.2.7.13. Temperature Regulation

Hypothermia occurs with 87% of patients on clozapine (69). This effect, considered benign, is believed to be a CNS effect.

Hyperthermia
A benign temperature elevation of 1–2 °F has been noted within the first 5–20 days of treatment with clozapine. It is estimated to occur in 7–14% of patients. The temperature increase might indicate a possible infection secondary to leukopenia or, possibly, NMS. Patients with hyperthermia should have a CBC and sedimentation rate done to rule out infection and should be followed for signs of NMS. Typically, this resolves without treatment or clozapine discontinuation. Antipyretics (i.e., acetaminophen) effectively lower the temperature (558).

34.1.3. First-Generation Antipsychotics

The primary FDA-approved indications for FGA are schizophrenia, mania, and Tourette's syndrome.

34.1.3.1. Efficacy

34.1.3.1.1. Schizophrenia

FGA have shown to be effective for patients with first-episode and chronic schizophrenia (9). Relapse rates ranged from 60% to 90% in two to three year follow-up studies of patients with diagnoses of first-time psychosis. Although this rate is high, patients might be given a trial off antipsychotics after a 1- to 2-year period, if asymptomatic, to determine continuing need (14). A longer maintenance period would be warranted with relapse after discontinuation, or continuous symptomatology while receiving medication.

34.1.3.1.2. Schizophrenia Maintenance Treatment

Maintenance antipsychotic treatment in patients who have experienced two or more relapses is effective (70). For patients diagnosed with schizophrenia who meet this criterion, 68% on placebo will relapse within the first year after hospitalization, and an additional 65% of remaining patients will relapse the following year, as compared to a first- and second-year relapse rate of 41% and 15%, respectively, in patients treated with maintenance antipsychotics for 2 years. There are no consistent predictors to characterize patients who will maintain in remission from those who will relapse (71). Although antipsychotics have great importance in preventing relapse and possible rehospitalization, the high percentage of patients on drug treatment who do relapse suggests that nonpharmacological factors (e.g., social and family environment) are also important (10). Antipsychotic prophylaxis in combination with social interventions offers the best prognosis for these patients (72).

34.1.3.1.3. Refractory Schizophrenia

Patients who do not respond or partially respond to FGA after a 4-week initial course may be managed by one of the following: 1) continuing the same FGA at the same dose; 2) increasing the dose of the current FGA; 3) switching to a different class within the FGA group; 4) adding a second drug to the current antipsychotic (i.e., adjunctive treatment); or 5) switching to an SGA (3). A study of patients nonresponsive to fluphenazine for 4 weeks showed that maintaining the fluphenazine dose for an additional 4 weeks, raising the dose, or switching to haloperidol resulted in a non-significant increase in response rates of 5%, 13%, and 8%, respectively. No studies have directly compared the above strategies with adjunctive treatments. Of all adjunctive agents used, lithium, carbamazepine, benzodiazepines, and reserpine are associated with more positive outcomes. However, there are not extensive amounts of data to support their use. Other adjunctive treatments reported to be useful but overall less effective

than the agents discussed thus far include clonidine, propranolol, valproate, verapamil, and levodopa (73–75). The response rate to antipsychotic combination therapy ranges from 4 to 30%, including two FGA, one FGA and one SGA, and two SGA or more (76). There is limited evidence to suggest that using ≥ 2 antipsychotics simultaneously are better than one if equivalent doses are used (71, 76). In fact, an increase in ADR, cost of drug therapy, and length of hospitalization without a demonstrated increase in therapeutic response may occur (77, 78). The practice of combining two or more FGA is not recommended unless the patient has failed a clozapine trial and individual trials of the respective agents.

34.1.3.2. Schizoaffective Disorder

Lithium is the primary treatment for schizoaffective disorder, and antipsychotics are used in combination with lithium when psychotic symptomatology is prominent (79). Most studies report improvement in psychotic symptoms in schizoaffective patients receiving antipsychotics. Because of diagnostic variability among studies and, generally, small sample sizes, the response rate is not known.

34.1.3.3. Mania

FGA serve an adjunctive role in the acute treatment of mania (80). Most research has been with chlorpromazine and haloperidol. Although any antipsychotic can be used alone or in combination with lithium for mania, studies indicate that antipsychotics, at least until therapeutic lithium levels are achieved, are better than lithium in suppressing psychomotor activity, hostility, excitement, grandiosity, and suspiciousness. Once lithium levels are therapeutic and clinical response is attained, the antipsychotic dose can be tapered and ultimately discontinued. Several studies report that the addition of a benzodiazepine may reduce antipsychotic dose requirements in mania (81). The efficacy of antipsychotics in the prophylactic, or maintenance treatment of bipolar illness has not been extensively evaluated in controlled trials. However, a survey of the literature indicates this is sometimes done clinically (80). Two controlled studies of depot antipsychotics not available in the United States reported that some patients benefited from long-term treatment (82). FGA are generally not recommended for long-term management of bipolar illness because of concerns about tardive dyskinesia (83).

34.1.3.4. Cognitive Disorders

Medications are sometimes needed to control psychotic symptoms or behavioral disturbances when patients with cognitive disorders become hostile, agitated, aggressive, and dangerous to themselves and others. FGA are modestly effective in managing these symptoms in the management of patients with cognitive disorders (i.e., dementia) or delirium (30).

34.1.3.5. Dementia

The use of antipsychotic medications is regulated in long term care facilities, rising from concerns about inappropriate use and potential ADR such as tardive dyskinesia, orthostatic hypotension, and anticholinergic delirium. The Omnibus Budget Reconciliation Act (OBRA) of the Health Care Financing Administration, a government agency that regulates Medicare and Medicaid recipients, went into effect October 1, 1990. This act stated that appropriate indications for antipsychotics would include dementia and delirium with associated psychotic and/or agitated behaviors that 1) are quantitatively and objectively documented, 2) are not the result of preventable factors, and 3) are causing the patient to present a danger to him- or herself or to others. In addition, antipsychotics may be used in patients with psychotic symptoms that are not exhibited as dangerous but that cause them distress or impairment in functional capacity. There is no evidence to suggest that antipsychotics reverse memory impairment, intellectual deterioration, or confusion, even in psychotic patients. However, meta-analyses of double-blind, placebo-controlled studies of inpatients with dementia and severe behavioral disturbances reported improvement, as the average response rates to antipsychotics and placebo were 59% (range 0%—67%) and 41%, respectively (84, 85). Although the specific symptoms responding to antipsychotics could not be determined, it was concluded that agitation, uncooperativeness, and hallucinations were more likely to improve with medication. All antipsychotics are equally effective for treating psychosis or behavioral disturbances (84). Therefore, individual response and the fewest undesirable effects usually determine drug selection.

34.1.3.6. Dosage

All FGA are equally effective in treating psychotic disorders when given in equipotent doses (10). For example, chlorpromazine 100 mg is approximately equal in therapeutic use to trifluoperazine 4 mg, thioridazine 100 mg, fluphenazine 2 mg, thiothixene

TABLE 34.1 Potency classification and approximate equivalent doses of high- and low-potency FGA and SGA. Oral doses equivalent to chlorpromazine 100 mg.

Low potency FGA	High potency FGA	SGA
Chlorpromazine (100)	Fluphenazine (2)	Risperidone (2)
Mesoridazine (50)	Haloperidol (2)	Olanzapine (5)
Thioridazine (100)	Loxapine (10)	Aripiprazole (7.5)
	Molindone (10)	Ziprasidone (60)
	Perphenazine (8)	Quetiapine (75)
	Thiothixene (5)	Clozapine (50)*
	Trifluoperazine (4)	Asenapine (6.5)
		Lurasidone (25)
		Iloperidone (5)
		Paliperidone (3)

*Dose changes made by the editor.

3 mg, or haloperidol 2 mg (71). FGA can be divided into low (eg, chlorpromazine) or high-potency (eg, perphenazine, haloperidol, thiothixene) compounds based on their relative oral potency (see Table 34.1) (86). This classification is important in predicting some ADR such as orthostatic hypotension, sedation, anticholinergic effects and weight gain which are more likely to occur with the high potency FGA, although it is important to note that many antipsychotics have not been directly compared in regard to ADR. When switching a patient from one antipsychotic to another, Table 34.1 has been constructed to estimate the interdrug milligram potencies of the typical antipsychotic drugs. The average dose of chlorpromazine was 734 mg $\pm$ 63. Thus, if the relative potency value for an antipsychotic is multiplied by a factor of 7.34, the resulting product will be the mean dose reported in the efficacy studies. This is a reasonable prospective estimation of the initial target dose the clinician should aim for when first dosing new acutely ill schizophrenics patients if not utilizing either haloperidol or clozapine blood levels to dose the patient.

34.1.3.6.1. Schizophrenia, Nonagitated patient

A dose of chlorpromazine 300 mg/day (oral) or its equivalent is considered a minimal therapeutic dose for the treatment of acute psychosis. Peak response occurred at approximately chlorpromazine 600 mg/day or its equivalent in dose-response studies of schizophrenic patients (87). Doses of chlorpromazine >1200 mg/day or its equivalent do not produce substantially greater improvement than smaller doses (71, 87). Also, haloperidol dosed between 3 mg and 7.5 mg daily were found to be equally efficacious and being associated with fewer ADR than, higher doses (88). However, patients respond to widely differing dosages, and target symptom management will be significant in finding an adequate dose for individual patients. An acutely psychotic, not uncontrollably agitated, patient can generally be started on chlorpromazine 100 mg or its equivalent administered two or three times daily. Gradual dose titration may occur at a rate of chlorpromazine 100—200 mg/day or its equivalent until clinical response is achieved, the upper limit of the recommended dose range is reached, or intolerable ADR occur. Divided doses may be switched to once daily (usually at bedtime) a week after a stable dose is achieved. Because of the slow response time associated with these agents, an antipsychotic must be given an adequate therapeutic trial. Patients should initially receive chlorpromazine doses of less than 800 mg/day or its equivalent, based on a study showing no significant difference between doses higher than 800 mg/day compared to doses lower than 800 mg/day (87).

34.1.3.6.2. Schizophrenia, Agitated Patient

The treatment of an agitated patient should achieve two goals. The immediate goal of treatment of acutely psychotic agitated patients is to reduce agitation, irritability, and/or hostility so that patients are not a physical danger to themselves or others (89). Alleviating the delusions and/or hallucinations that are assumed the basis of the agitated behavior is the ultimate goal. The technique of titrating the antipsychotic dosage against the patient's psychotic symptomatology by administering a series of a closely spaced parenteral doses over a period of hours is termed "rapid neuroleptization" (89). Because of the risk of mental status impairment and significant EPS associated with high-dose antipsychotic treatment, this technique should be reserved only for agitated patients who do not respond to conventional doses of antipsychotics. This technique, first used in 1963, dictates that the patient receives chlorpromazine 100 mg orally or 25 mg intramuscularly (or its equivalent) every 1–2 hours until agitation/psychosis are under control. As stated above, chlorpromazine greater than 800 mg (oral dose) daily is rarely recommended or needed. Haloperidol is a recommended agent, since it has an improved cardiovascular ADR profile (hypotension) over chlorpromazine. Dose administration of haloperidol 2 to 10 mg orally or intramuscularly (with dose correction) every 30 minutes to two hours has been recommended. Although haloperidol has been commonly used, evidence suggests other high-potency agents are equally safe and effective (90). After intramuscular treatment, the oral dose of the antipsychotic should be

equivalent to the total parenteral dose administered over the preceding 24 hours, corrected for bioavailability differences (90). The intramuscular:oral ratio for chlorpromazine is 1:4 (e.g., 25 mg IM equals 100 mg PO) and haloperidol is approximately 1:2 (e.g., 2.5 mg IM equals 5 mg PO).

34.1.3.6.3. Megadosing

Megadosing was not superior to conventional dosing in a review of 11 double-blind studies (91), and many of the studies reported that EPS were more common in the high-dose group. A later review of 33 studies agreed with the earlier recommendations (87). Patients who tolerate standard doses without significant clinical improvement might be considered for a high-dose treatment protocol before changing antipsychotics (92).

34.1.3.6.4. Schizophrenia, Maintenance Dosing

Patients who have demonstrated a relapse after drug discontinuation may be considered candidates for long-term antipsychotic treatment. FGA have a slow onset of action, which makes a direct correlation between a given dose, and therapeutic outcome difficult to determine. Therefore, many patients will receive higher than necessary doses during acute exacerbations of their illness, which will produce an increase in side effects (e.g., extrapyramidal) (10).

34.1.3.6.5. Oral FGA

Two different oral dosing strategies—intermittent, or "targeted," treatment and continuous minimal dosing—have been recommended for maintenance treatment (3, 10). Continuous minimal dosing is the recommended treatment regimen. With intermittent treatment, an attempt is made to reduce total drug exposure by treating the patient only when active symptoms are present. Under the continuous minimal dosing strategy, patients chronically receive lower doses than were used during acute treatment. This approach is based on the observation that many patients do not relapse when their dose is significantly reduced after acute treatment (93, 94). Comparisons of targeted treatment and low-dose continuous dosing strategies found that targeted treatment was associated with an increased risk of symptomatic relapse (10, 95). Some studies have reported that drug holidays increase the risk of tardive dyskinesia (96), whereas low-dose continuous treatment may reduce the risk of tardive dyskinesia (94).

After a patient has been stabilized on an antipsychotic for 3–6 months, dosage reduction should be considered (94). Dosage reductions should occur at a rate of 20% every 6 months to achieve the minimal effective dose (94). A review concluded the majority of patients can be maintained on 300–600 mg/day of chlorpromazine (or equivalent) (87).

34.1.3.6.6. Long-Acting Parenteral Antipsychotics (LAPA)

A review of five studies that lasted more than 9 months reported that noncompliance with orally administered antipsychotics averaged 33% (3). Because constant drug intake is important in preventing symptom relapse and rehospitalization, long-acting parenteral antipsychotics (LAPA) have been recommended for patients who are repeatedly noncompliant with oral medication. Fluphenazine decanoate is preferred to fluphenazine enanthate because of a lower incidence of ADR and a longer duration of action (97). Most clinicians recommend that patients being considered for a decanoate dosage form have their treatment initiated with an oral antipsychotic (98). Patients receiving oral antipsychotics other than fluphenazine or haloperidol should have their antipsychotic converted to the respective drug using relative oral potency (see Table 34.1). Thus a patient receiving perphenazine 60 mg/day orally is receiving the equivalent of 12 mg/day of haloperidol. The rationale is that the oral form allows flexibility in daily dosing and the ability to quickly withdraw the drug if "significant" ADR occur. However, this practice requires the patient to be converted from oral to decanoate dosage form after clinical improvement. Typically, the patient who responds to an oral drug will be administered one or two injections of the decanoate as an inpatient with plans to taper the oral dose as an outpatient over a variable time. However, once discharged, the patient may be noncompliant with the oral drug. This may significantly affect the total serum concentration of the antipsychotic, potentially leading to relapse. Likewise, noncompliance with the oral drug may lead to confusion about the required maintenance dose if the patient is continuously prescribed both the oral and depot antipsychotic (99). Therefore, long-term use of this combination of dosage forms is not recommended.

The literature on conversion of oral fluphenazine to decanoate indicates a wide variability in recommended doses (98). Due to assay technical difficulties and significant interpatient variability in oral fluphenazine first-pass metabolism, serum concentration data comparing oral with decanoate doses indicate a poor relationship (98). Typical starting doses for fluphenazine decanoate range from 6.25 to 25 mg every 2 weeks (98). Although loading doses of fluphenazine decanoate might alleviate the

need for continuing oral fluphenazine during the conversion, this approach has not been investigated. A review of four studies concluded that fluphenazine decanoate 10–30 mg every 2 wk provides the greatest protection against relapse. Interestingly, 45 mg every 2 wk was associated with a worse outcome (87). Fluphenazine decanoate has typically been administered on a weekly or biweekly schedule. One study reported that 30% of the patients could be successfully maintained when the drug was given at 3-week intervals and 30% were maintained on monthly injections up to 1 year (99). In a later study, 30% of the patients were managed with monthly injections over an 8-month period (100). Patients stabilized on fluphenazine decanoate should be considered for an increased interval between injections as a dose reduction strategy. Fluphenazine decanoate 10—30 mg every 2 weeks provides the greatest protection against relapse (87).

Haloperidol oral to decanoate conversion presents similar concerns as fluphenazine. However, the metabolic pattern of haloperidol is less complicated (101, 102). Conversion recommendations based on haloperidol oral doses with and without a loading dose of the decanoate have been reported. Usual haloperidol decanoate dose ranges are 75—300 mg/month, although doses of 500 mg/month have been used. Patient conversion from oral haloperidol to maintenance doses has been accomplished with and without the use of a haloperidol decanoate loading dose. The non-loading-dose approach involves administering a calculated maintenance dose while the oral dose is tapered. A review of U.S. studies indicated that a maintenance dose of decanoate (mg/month) to oral (mg/day) dose ratio of 10–15 was more reasonable than the European literature's ratio of 20 (101). For example, using the U.S. studies' recommendations, if a patient was stabilized on 20 mg/day oral, the decanoate dose would be 200 mg administered every month. Considering that steady-state haloperidol concentrations are not reached for 3 months with the decanoate, a tapering schedule of oral haloperidol over a 1-month period might be attempted. If side effects occur during this period, acceleration of the oral taper might be considered. Loading doses of haloperidol decanoate of 20 and 40 times the stabilized oral dose have been investigated. Although both were effective, the higher dose was associated with more EPS (101). A loading dose protocol for initiating haloperidol decanoate treatment has been recommended (3). In the elderly (i.e., persons more than 65 years of age) and in patients on 10 mg/day or less of oral haloperidol, the recommended loading dose is 10—15 times the oral dose (3). If a patient is receiving 10 mg/day of oral haloperidol, the total loading dose is 20 times oral dose. Although an initial maximum decanoate dose of 100 mg is recommended, higher initial doses can be used (3, 103). For example, a 300-mg total loading dose would be administered as 100 mg with the 200-mg dose administered 3—7 days later. The oral haloperidol is discontinued at the time of the first injection of the loading dose or, more conservatively, at the time of the final loading dose. The target maintenance dose is 50% of the loading dose. To achieve the maintenance dose, the second month's dose can be reduced by 25% and the third month's dose by an additional 25%. In older patients, the target maintenance dose would still be 50% of the loading dose. The maximum recommended haloperidol decanoate dose is 450 mg/month (3). Earlier studies have reported haloperidol doses of 50 mg-225 mg. A later study reported that with haloperidol decanoate monthly maintenance doses of 200 mg, 100 mg, 50 mg, and 25 mg the relapse rates were 15%, 23%, 25%, and 60%, respectively (72, 93). Although a 200-mg monthly dose was associated with the lowest relapse rate, almost 75% of patients treated with 50 mg or 100 mg per month did not relapse. It is important to note that these patients may have been at a low risk of relapse (3). A significant level of drug remains in tissues for weeks to months after depot drug discontinuation (100, 104, 105), so the delay in relapse after dose reduction makes determining the lowest effective dose difficult.

An undocumented recommendation indicated that dosage reduction of fluphenazine or haloperidol should not exceed 10% every 3 months (100), but a dosage reduction period of at least 6 months would be preferable (94). One study of fluphenazine decanoate suggested that if a patient demonstrates initial signs of relapse during dosage reduction or with maintenance doses, oral doses of fluphenazine 10 mg/day might be added (95). The fluphenazine decanoate dose could then be increased by 2.5—5 mg every 2 weeks and a trial discontinuation of the oral drug attempted after 1 month. The same strategy could be applied to haloperidol decanoate using supplemental oral haloperidol doses of 10 mg/day while the decanoate dose was increased by 25—50 mg every month.

One difficulty in determining the lowest effective maintenance dose for depot antipsychotics is the delay in symptom relapse after dose reduction. Several studies have demonstrated that after drug discontinuation, significant concentrations of the drug remain in the tissues for weeks to months (104–106). A decrease in serum prolactin concentrations may take longer (104, 106). A recent undocumented recommendation suggested that a dose reduction of fluphenazine or haloperidol should not exceed 10% every 3 months (100). This recommendation might produce a better correlation between dose and onset of relapse symptoms.

Three studies report haloperidol to fluphenazine decanoate dose ratios of 1.4:1, 3:1, and 7:1 (100, 106, 107). However, the use of supplemental oral antipsychotics in these reports makes direct comparisons difficult. The 3:1 ratio would be a reasonable starting point. Subsequent dose adjustment should be based on therapeutic response and ADR.

34.1.3.7. Cognitive Disorders

34.1.3.7.1. Dementia

Dementia patients may be unusually sensitive to FGA therapeutic and ADR; therefore, low doses are initially used in this population (85, 108, 109). In one review, final doses (expressed in chlorpromazine equivalents) ranged from 66 to 267 mg/day (31). Dose titration is dependent on therapeutic response and ADR.

34.1.3.8. Adverse Effects

The ADR of FGA antipsychotics can be classified as allergic, autonomic, cardiovascular, dermatologic, endocrine, hematologic, hepatotoxic, metabolic, neurologic, ophthalmologic, overdosage, and sexual dysfunction. Common ADR involve the autonomic (i.e., hypotension) and neurologic (i.e., sedation, extrapyramidal) systems. Relatively more sedative and vascular effects are seen with low-potency FGA (i.e., chlorpromazine, thioridazine, mesoridazine, chlorprothixene) as compared to more extrapyramidal side effects (EPSE) with high-potency FGA (i.e., haloperidol, perphenazine, fluphenazine, thiothixene) (110, 111).

34.1.3.8.1. Autonomic

The autonomic nervous system effects are due to autonomic hyperactivity (antipsychotic withdrawal) and cholinergic blockade (anticholinergic activity).

Anticholinergic ADR of antipsychotics can occur as either central effects or peripheral effects. Peripheral effects, including dry moth, eyes, and throat, blurred vision, mydriasis, tachycardia, constipation, urinary retention and paralytic ileus, and CNS effects such as delirium depend on the anticholinergic potency of the individual agent. Patients may develop tolerance to dry mouth and some of the other anticholinergic ADR; however, some patients will continue to experience these effects. Constipation is a common ADR and should be monitored.

Withdrawal or rebound symptoms may be reported upon abrupt discontinuation of FGA. Symptoms such as insomnia, headache, hypersalivation, diarrhea, nausea, and vomiting have occurred. Symptoms may begin 2–3 days after discontinuation, and may occur for up to two weeks. The incidence of withdrawal symptoms is 10–75%. Patients prescribed FGA for at least one month should undergo a taper of antipsychotic upon discontinuation.

34.1.3.8.2. Cardiovascular

Orthostatic hypotension usually occurs during the first few hours or days of treatment. Patients receiving low-potency antipsychotics should be counseled to rise from bed gradually, sit at first with legs dangling, wait for a minute, and then rise only if there is no feeling of dizziness or faintness (112, 113). If hypotension is severe or tolerance does not develop, the medication may be changed to a high potency FGA or a SGA less likely to cause the effect.

Electrocardiogram (ECG) changes have been reported. Low potency FGA have been commonly reported to produce broadened, flattened T waves and an increase in the QR interval. This finding is of uncertain clinical significance. There are similar reports with chlorprothixene, loxapine, molindone, and thiothixene. The labeling of thioridazine and its metabolite mesoridazine now include a black box warning because of several case reports of torsade de pointes (a re-entry arrhythmia manifested by QTc prolongation that can result in ventricular tachycardia) and sudden death associated with thioridazine use (114). Thioridazine's effect on mean maximum increasing QTc interval after a 50 mg dose was 23 ms (115). Thioridazine should be reserved for the treatment of patients with symptoms that have failed other medications, and baseline ECG and serum potassium levels are recommended for patients at baseline and periodically during treatment. Patients with QTc > 450 ms should not be initiated with thioridazine, and if QTc > 500 ms, patients should be discontinued. The FDA also recommends that patients taking pimozide should undergo baseline ECG and periodic follow-up (116–118).

34.1.3.8.3. Dermatologic

Simple allergic skin reactions are manifested in three forms. The most common, a maculopapular rash on the face, neck, or upper chest and extremities, occurs in 5–10% of patients taking chlorpromazine within 14–60 days after the start of therapy. Other reactions include erythema multiforme, localized or generalized urticaria, angioneurotic edema and exfoliative dermatitis (112, 113).

Photosensitivity reactions have been reported to occur in 3% of patients taking FGA, with most cases related to chlorpromazine (112, 113). Patients should wear protective clothing and/or sunblock with a maximum SPF rating.

Long-term skin effects of FGA include pigmentary skin changes. Pigmentary changes include a tan color that progresses to a slate gray, metallic blue, or purple color over the areas of the skin exposed to sunlight. The frequency of bluish pigmentation is approximately 1% with FGA. Pigmentation is related to cumulative dose ingested, thus the low-potency FGA are thought to be associated with a higher incidence of pigmentation effects as opposed to high-potency FGA. Haloperidol reportedly does not cause this ADR (112, 113).

34.1.3.8.4. Endocrine

ADR include amenorrhea, galactorrhea, and gynecomastia, which are thought to be related to prolactin level elevations caused by antipsychotic agents (71, 112, 119). Amenorrhea is reported to occur in 18–95% of women receiving FGA compared with 3–5% of the general female population (120). Galactorrhea most commonly occurring in women is frequently accompanied by some degree of breast enlargement or engorgement. One study reported an incidence of 57% in women (121). Gynecomastia (breast enlargement) from any cause is uncommon; therefore, other medical causes should be considered. Gynecomastia in males has rarely been reported (119, 122).

Case reports and studies suggest that antipsychotics may contribute to water dysregulation, though polydipsia and intermittent hyponatremia have been reported to improve with antipsychotic treatment (123, 124). Future studies of FGA in short and long-term treatment of patients with hyponatremia are needed.

34.1.3.8.5. Hematologic

Leukocytosis, leucopenia and eosinophilia have been reported as transient effects of FGA, usually not requiring change in therapy. Agranulocytosis occurring rarely, has been reported with all antipsychotics, but most case reports involve patients receiving aliphatic and piperidine phenothiazines. If this occurs, management of psychosis with a different antipsychotic is recommended.

34.1.3.8.6. Hepatotoxicity

Mild and transient liver enzyme elevations have been reported with the FGA, and does not usually require discontinuation. Chlorpromazine has been associated with liver dysfunction although rarely. The reaction occurs within the first month of treatment, and includes jaundice, and laboratory findings that resemble those of cholestatic jaundice. It is recommended that the suspected offending agent be discontinued. The incidence of jaundice associated with phenothiazines is estimated to be less than 0.5%.

34.1.3.8.7. Metabolic

Weight gain has been reported frequently in low-potency FGA-treated patients, averaging 6 kg in a 6-week treatment period. Management includes exercise and dietary restriction. Molindone and loxapine have been associated with weight loss during treatment but this has not been conclusively demonstrated. Amphetamine-like appetite suppressants should not be prescribed, due to the potential to exacerbate psychosis (113, 125).

34.1.3.8.8. Neuroleptic Malignant Syndrome (NMS)

Although there is substantial variability among cases of NMS, most cases commonly exhibit muscle rigidity, hyperpyrexia, altered consciousness, and autonomic instability (labile blood pressure, tachycardia, and tachypnea) (126). The reported incidence varies from 0.02 to 3.23% (127). Ninety percent of the patients who developed NMS did so within 10 days of drug initiation (128). The overall mortality rate for cases reported between 1959 and 1987 was 18.8%. Since 1984, the rate has decreased to 11.6% (129). Later reports have not mentioned fatalities, but they may still occur. Patients with myoglobinuria and renal failure have a mortality rate of 47 and 56% respectively. Other complications, such as seizures, pulmonary embolus, or disseminated intravascular coagulation have lead to death. When NMS is suspected, the antipsychotic should be discontinued and supportive care instituted immediately. Intubation, mechanical ventilation, fever reduction, and other supportive measures may be required until the muscular rigidity and fever begin to resolve (128). Hydration is particularly important. The exact pharmacologic treatment of NMS has not been established. Supportive care combined with immediate discontinuation of the causative agent is the primary treatment of NMS. In addition, specific drug treatments such as bromocriptine or dantrolene are frequently used. If possible, it is important to allow a period of two weeks after an episode of NMS has completely resolved before reinitiating antipsychotic treatment. Use of a different antipsychotic may minimize the risk of recurrence of NMS. Although the literature does not support the conclusion that lithium increases the risk of NMS, close monitoring is recommended if lithium is used.

TABLE 34.2 Pharmacotherapy for extrapyramidal side effects (EPS).

EPS	Drug and dose
Dystonia	Diphenhydramine 50 mg or benztropine 2 mg IV or IM stat, may repeat IV dose in 5 minutes and IM dose in 20–40 minutes
Akathisia	Benztropine 2–6 mg po q HS
	Propranolol 10–40 mg po bid
	Diazepam 5–10 *mg po mg tid or qid
	Amantadine 100–200 mg po* either once or twice daily
	Clonidine 0.1–0.4 mg po bid
Parkinsonism	Benztropine 1–4 mg po qd–qid*
	Trihexyphenidyl 2–5 mg po bid–qid*

*Dose changes made by the editor.

34.1.3.9. Neurologic

34.1.3.9.1. Cognition

A review of the published literature reported that FGA do not have significant effects on memory, with the exception for potentially causing ADR in certain patients (130).

34.1.3.9.2. Extrapyramidal Side Effects (EPS)

They are divided into early- and late-onset types. Early-onset symptoms usually occur within the first 4 weeks of treatment and include dystonia, parkinsonism, and akathisia. A summary of drugs and doses effective in the treatment of EPS is presented in Table 34.2. Late-onset types occurring after 6 months of treatment are represented by tardive dyskinesia, tardive dystonia, and tardive akathisia. Estimates of the incidence of EPS with antipsychotics vary widely, ranging from 2.2% to 95%. Much of the variation in the reported percentages may be explained by differences in the antipsychotic prescribed (low- versus high-potency), length of treatment, dosage, individual sensitivity, and definitions of EPS with the high-potency FGA causing higher rates of EPS. Dystonic reactions consist of involuntary tonic contraction of skeletal muscles of virtually any striated muscle group (112, 113). The most common dystonias involve the muscles of the head and face, producing buccal spasms, oculogyric crisis, facial grimacing, tics, or trismus. Involvement of the neck musculature produces torticollis or retrocollis. If the trunk is involved, shoulder shrugging, tortipelvis, opisthotonos, or scoliosis may occur. Carpopedal spasms, dorsiflexion of the toes, contraction of muscle groups of arms or legs, or a dystonic gait may be seen if the limbs are involved. Ninety percent of dystonic reactions occur by day 4 of antipsychotic treatment. They may occur after one dose of an antipsychotic regardless of the route of administration. They usually occur once, but occasionally recur when there is an increase in dosage. Although a dystonic reaction may occur at any age, it is more common in patients <35 years, and is twice as likely to occur in men. Dystonias usually are benign and disappear without treatment. However, because of the extreme discomfort to the patient and the possibility of serious sequelae, dystonic reactions are treated as soon after their appearance as possible. Many agents have been recommended to treat dystonias, but intravenous diphenhydramine 50 mg or benztropine 2 mg will reverse the dystonia, usually within 2 minutes. If no relief occurs within 5 minutes, the dose should be repeated. The intramuscular route has been successfully used, but resolution of the dystonia may take 20–40 minutes (131). Akathisia refers to a subjective experience of motor restlessness. Patients may complain of an inability to sit or stand still, or a compulsion to pace (132). They may also complain of being restless and having to be in constant motion. While standing, they may rock back and forth or shift their weight from one leg to another. Patients may also suffer from initial insomnia because they cannot lie motionless in bed long enough to fall asleep. Typically, akathisia occurs within 2–3 weeks of initiation of the antipsychotic although some patients may develop symptoms within hours of the first dose. Ninety percent of the cases develop within the first 73 days of treatment. Akathisia tends to occur more frequently in the middle-aged, with women twice as likely to experience it. An accurate diagnosis is important because misdiagnosis may lead to an unnecessary increase in antipsychotic medication with worsening of the akathisia. Dose reduction or a change to an agent less prone to cause EPS (i.e., a low-potency drug) may alleviate the need to add a pharmacologic agent. Upon discontinuation, akathisia symptoms generally resolve in 7 days, but may take several weeks. Propranolol may be useful in antipsychotic-induced akathisia (133). Most studies reported that anticholinergics were effective for akathisia in patients with concomitant drug-induced parkinsonism. Therefore, anticholinergics might be considered first-line treatment for those occurrences. Benzodiazepines (BZD) may be beneficial, as the majority of studies demonstrated positive results in patients with akathisia (133). The parkinsonian ADR presents as tremor, rigidity, hypokinesia or akinesia, individually or in combination (112, 113). Drooling, an accelerating gait, oily skin, dysarthria, and dysphagia may accompany the symptoms. Akinesia may

present early as slowness in initiating motor tasks and fatigue when performing activities requiring repetitive movements (bradykinesia). Affected persons appear apathetic with little facial expression, have difficulty walking, and their handwriting may take on a cramped appearance (micrographia). This drug-induced condition can be misinterpreted as depressive symptomatology. The typical antipsychotic-induced parkinsonian tremor may be present during movement as well as at rest. Tremor usually begins in one or both upper extremities and in severe cases may involve the tongue, jaw, and lower extremities. The tremor may involve the mouth, chin, and lips, which has been termed the "rabbit syndrome." Cogwheel rigidity, in which a ratchet-like phenomenon can be elicited upon passive movement of a limb, is the result of the presence of both rigidity and tremor. Parkinsonism occurs at varying intervals after the initiation of antipsychotic drug therapy, but usually occurs within 4 weeks. Like akathisia, parkinsonism is usually dose and patient related. Drug-induced parkinsonism tends to occur most often in the elderly, with women twice as likely to develop it as men. Treatment of antipsychotic-induced parkinsonism includes dose reduction, changing to an agent less likely to produce EP (i.e., low-potency drug), addition of conventional anticholinergics such as benztropine, or addition of amantadine. The condition disappears upon discontinuation of drug therapy, but this may take several weeks to months depending upon the dosage and individual patient.

Tardive dyskinesia (TD) is a complex syndrome of hyperkinetic involuntary movements (112, 113). All antipsychotics have been associated with TD, but real differences in incidences among antipsychotics, if they exist, are not obvious. These syndromes wax and wane over time, disappear during sleep, and are exacerbated by emotionally disturbing experiences (112, 113). The most widely described symptoms make up the buccolinguomasticatory triad, which consists of (1) sucking and smacking movements of the lips, (2) lateral jaw movements, and (3) puffing of the cheeks, with the tongue thrusting, rolling, or making fly-catching movements. Such movements may be carried on with the mouth closed with bites of the tongue and inside of the cheek as well as a chewing movement. The extremities may show choreiform movements that are variable, purposeless, involuntary, and quick. Frequently associated with these symptoms are athetoid movements, which are continuous, arrhythmic, wave-like slow movements in the distal parts of the limbs. Axial hyperkinesia (i.e., to-and-fro clonic movement of the spine in an anterior-posterior direction) and ballistic movements (i.e., rhythmical side-to-side swaying) also may be present. All involuntary movements, exacerbated by emotionally upsetting situations, disappear during sleep. Drug-induced parkinsonism is present in 30–40% of patients with TD (134). Although tardive dyskinesia usually is recognized after more than a year of treatment, onset within 6 months of initiation of antipsychotics has been reported. Tardive dyskinesia has been reported in patients exposed to virtually all classes of antipsychotics. The prevalence of tardive dyskinesia, corrected for spontaneous dyskinesia, averages 15–20%. The incidence is estimated at 2–5% per year over 5–6 years of treatment (135, 136). The prevalence, when corrected for a spontaneous dyskinesia rate of 1% to 5%, averages 15% to 20%. Increased prevalence of tardive dyskinesia is associated with the following factors: age, gender, psychiatric diagnosis, antipsychotic dose, and duration of antipsychotic exposure. TD usually has an insidious onset while the patients are still receiving antipsychotics, although abnormal movements often appear for the first time or increase dramatically following a reduction in dose or discontinuation of the drug. Despite discontinuation of the antipsychotic, the dyskinesia is potentially irreversible. Several studies indicated that, although antipsychotics are continued, TD movements are not generally progressive and may improve or resolve (135, 137). Many agents have been utilized in attempting to treat TD, but these agents have produced only inconsistent and temporary improvement. The only treatment recommendation is discontinuation of the medication. The prolonged use of antipsychotics should be restricted to situations in which there are compelling indications, (e.g., schizophrenia). Whether to discontinue antipsychotics in patients with schizophrenia is a matter of clinical judgment. The use of antipsychotics should be supported with a proper indication, demonstrated response (preferably with drug discontinuation), dose minimization, informed consent, and a structured assessment (e.g., Abnormal Involuntary Movement Scale) performed at least yearly for tardive dyskinesia (137–139).

34.1.3.9.3. Sedation

It occurs in the first few days of treatment. Patients may develop tolerance to this effect within several weeks. All available antipsychotics can cause sedation; however, the low-potency FGA are more sedating. This effect can be minimized by administering the total dose of antipsychotic at bedtime (112, 113).

34.1.3.9.4. Reduction of Seizure Threshold

All available antipsychotics reduce the seizure threshold. Generalized and focal motor seizures have been reported, but the incidence is $<1\%$. In general, antipsychotic-induced seizures do not pose a management problem. Patients develop tolerance to this effect and seizures will continue to occur only if higher doses are used. Seizure activity usually occurs as an early complication in treatment (112, 113).

34.1.3.9.5. Ophthalmologic

Cornea and lens changes have been noted with chlorpromazine, trifluoperazine, perphenazine, fluphenazine, chlorprothixene, and thiothixene (112, 113). Chlorpromazine is most clearly associated with these changes, which are related to a total lifetime dose of 1–3 kg. Vision usually is not impaired. Cornea and lens changes appear to be positively correlated with severe photosensitivity response to chlorpromazine. Pigmentary retinopathy is primarily associated with thioridazine, although it has been reported with chlorpromazine (112, 113). The relationship appears to be a function of time and dose, rather than dose accumulation. Thioridazine $\leq$ 800 mg/day has been defined as safe. When thioridazine causes retinal pigmentation, a drastic reduction in visual acuity and even blindness may result. Treatment is discontinuation and substitution of another antipsychotic.

34.1.3.9.6. Psychiatric

Delirium secondary to antipsychotics occur infrequently, but may occur more commonly in patients treated with agents with anticholinergic effects such as chlorpromazine and thioridazine. This is thought to be more common if an antipsychotic is combined with another anticholinergic agent, especially in elderly patients. Although "supersensitivity psychosis" after long-term antipsychotics and rebound psychoses after drug discontinuation have been suggested, conclusive evidence that this is related primarily to drug treatment is lacking (140).

34.1.3.9.7. Sexual Disturbances

In males the disturbances include ejaculatory dysfunction, impotence, reduced libido, and priapism. Ejaculatory disturbances have been attributed to thioridazine, chlorpromazine, mesoridazine, and chlorprothixene. At lower antipsychotic doses, ejaculation may be delayed or completely blocked without interfering with erection. Patients report absence of ejaculation and, occasionally, suprapubic pain on orgasm. This effect may be dose related, so dose reduction might be tried. If this fails, a high-potency, nonphenothiazine (i.e., thiothixene, haloperidol) might be substituted. Impotence and decreased libido have been associated with chlorpromazine, fluphenazine decanoate, haloperidol, pimozide, thioridazine, and thiothixene. Management might include dose reduction and drug substitution as indicated for ejaculatory disturbances (141). Antipsychotic-induced priapism (a prolonged painful erection) is associated with chlorpromazine, fluphenazine, haloperidol, mesoridazine, molindone, perphenazine, thioridazine, and thiothixene (142). It does not appear to be dose related. Priapism is considered a medical emergency. Prompt discontinuation of the antipsychotic is necessary, although reversal may not occur with antipsychotic discontinuation. Without resolution of the erection, it is reported that 18–80% of patients will become impotent. Management includes substitution of an antipsychotic of a different chemical class and close monitoring.

34.1.3.9.8. Temperature Regulation

Temperature regulation may be altered by inhibition of hypothalamic control area, and it has been demonstrated that patients receiving antipsychotics may not maintain normal body temperature on exposure to cold or heat (127).

34.1.3.9.9. Urinary

Enuresis or urinary incontinence has been associated with antipsychotics, and onset is often within two weeks of initiating treatment. Urinary retention may also occur, especially with medications having higher anticholinergic effects.

34.2. Depression

Antidepressants are the mainstay of pharmacotherapy for depression. Although little efficacy data separate them, the ADR profiles and drug-drug interaction profiles differ greatly. The selective serotonin reuptake inhibitors (SSRI) are the most widely used antidepressant class marketed today.

34.2.1. Selective Serotonin Reuptake Inhibitors

Since the release of fluoxetine in 1988, six of the SSRI have been marketed in the United States. These agents include fluoxetine, fluvoxamine, paroxetine, sertraline, citalopram, and its S-enantiomer, escitalopram. The primary indication for these agents is for the treatment of major depressive disorder; however, SSRIs have been shown efficacious for a myriad of other

disorders. Fluoxetine is FDA-approved for the treatment of major depressive disorder, bulimia nervosa, obsessive-compulsive disorder, panic disorder, and premenstrual dysphoric disorder, and has also shown efficacy for the following off-label disorders: major depressive disorder associated with alcoholism, major depressive disorder associated with diabetes, seasonal affective disorder, posttraumatic stress disorder, obesity, hot flashes, migraine, headache prophylaxis and fibromyalgia. Paroxetine is FDA-approved for the treatment of major depressive disorder, generalized anxiety disorder, obsessive-compulsive disorder, panic disorder, post-traumatic stress disorder, premenstrual dysphoric disorder and social phobia. Sertraline is FDA-approved for the treatment of major depressive disorder, obsessive-compulsive disorder, panic disorder, post-traumatic stress disorder, premenstrual dysphoric disorder, and social anxiety disorder. Fluvoxamine is FDA-indicated for the treatment of obsessive-compulsive disorder. Citalopram is FDA-indicated for the treatment of major depressive disorder. Escitalopram is indicated by the FDA for the treatment of major depressive disorder and generalized anxiety disorder.

34.2.1.1. Efficacy

A 1993 review of antidepressant efficacy studies estimated response rates of 54% and 47% for inpatients and outpatients using an intent-to-treat analysis (143). These response rates were similar to the tricyclic antidepressants (TCA), monoamine oxidase inhibitors (MAOI), and heterocyclic antidepressant rates. The inpatient response rate was 26% better than placebo while the outpatient response rate was 20% better than placebo. A meta-analysis comparing the efficacy of SSRI and TCA was performed (144). This meta-analysis showed no overall differences in efficacy between the two classes of agents. TCAs were shown to be more effective in depressed inpatients. SSRIs were better tolerated and discontinuation rates due to adverse drug reactions were less with SSRIs than TCAs. However, the number of patients needing to be treated with an SSRI to avoid a TCA discontinuation is calculated to be 33. This statistic indicates that there is an relatively small difference between SSRI and TCA dropout rates which makes it difficult for a clinician to notice this difference clinically. Controlled trials suggest that patients with longer depressive episodes experienced benefit of antidepressants over placebo or no treatment, while patients with shorter duration (1–6 months) did not (145–148). Older patients are thought to show a preferential response to TCA versus SSRI (149) especially in older women (150). It is suggested that men respond better to TCAs while women respond better to SSRIs (151).

34.2.1.1.1. Major Depression with Melancholic Features

SSRIs are less effective than TCAs in treating the melancholic subtype of MDD (65). Studies that used strict remission criteria showed TCA response rates of 57% to 63%, as compared to 8% to 30% for fluoxetine and 15% for placebo (152). It has been suggested that venlafaxine may also be more effective than SSRIs for melancholic depression (153). These studies suggest TCAs are superior to SSRIs in the treatment of melancholic depression.

34.2.1.1.2. Major Depression with Psychotic Features

Fluoxetine combined with perphenazine was effective in 73% of patients (n = 30) with psychotic depression. Paroxetine plus haloperidol or zotepine was effective in a 3-week trial. Finally, two larger trials (n = 251) concluded that after 8 weeks of treatment the remission rates for fluoxetine, versus a fluoxetine-olanzapine combination were similar (154–156).

34.2.1.1.3. Major Depression with Atypical Features

Fluoxetine, 20 to 60 mg/day, and imipramine, 50 to 300 mg/day, were more effective than placebo in studies of these agents in the treatment of "atypical depression". These findings differ from earlier data where TCAs were suggested to be inferior to MAOI (157–160).

34.2.1.1.4. Bipolar Disorder, Depressed Episode

A large controlled trial of lithium-treated patients found that paroxetine and imipramine were more effective than placebo in treatment groups when lithium levels were $\leq$ 0.8 mEq/L (161). Subsequently , the combination of olanzapine and fluoxetine was found to be superior to placebo and to olanzapine alone in the treatment of bipolar-I depression in a large 8-week trial (162). The olanzapine-fluoxetine combination has been FDA-indicated for the treatment of bipolar depression.

34.2.1.1.5. Treatment-Resistant Depression

Antidepressant treatment failures seem to be related to a number of factors that include an axis II diagnosis, prior treatment failure, the presence of delusions, and age 35 or younger. Compliance with medications is related to the frequency of antidepressant dose. It was found that only 7% of patients with depression missed doses on a once daily regimen, but more than 70%

of the patients, when prescribed a four times daily regimen, failed to take 25% to 50% of their prescribed dosage (163). It is recommended that the following order of pharmacotherapy interventions be used in attempting to treat treatment-resistant patients: 1) optimize treatment, 2) antidepressant substitution, 3) antidepressant augmentation, and 4) combination treatment. Patients experiencing some improvements in symptoms by week four should continue to week six of treatment, as many patients may become responders. However, if the patient has had no response by week four, a different antidepressant should be tried. Substitutions of a TCA to an SSRI have ranged from 43% to 75% in outpatient studies (164, 165). Switching between SSRIs resulted in mean success rates of 45% in a group of small, uncontrolled trials. A meta-analysis of three placebo-controlled trials of lithium augmentation in depression suggested that lithium augmentation improved the chances of response 3–4 fold (166). Among patients who failed a 12 week citalopram for major depression, The Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study reported a 30% remission rate among patients who had citalopram augmented with either bupropion or buspirone (167).

34.2.1.1.6. Continuation and Maintenance Therapy

It is likely that many patients with depression will eventually require a preventive maintenance treatment. Antidepressants and lithium have both been found to be effective in preventing recurrent unipolar depression. Lithium is more effective in the prevention of bipolar illness. Patients who have had two or more severe episodes of MDD should be considered for maintenance therapy (168). An increased relapse or recurrence rate has been reported in patients discontinuing medications before 6 months of treatment. Treatment should continue for an additional 4 to 6 months beyond the point of remission (168). Relapse rates, as reported in trials of SSRI maintenance treatment in prevention of depression in patients with recurrent major depression range from 6 to 26% for the SSRI and 43% to 57% for placebo (169, 170).

34.2.1.1.7. Mood Disorder Due to Medical Conditions

Symptoms of depression presenting in the medically ill may represent: 1) a major depressive episode which is independent of the medical condition; 2) an adjustment disorder with depressed mood precipitated by the stress of the medical illness; 3) secondary depression due to a preexisting medical condition felt to have pathophysiologic relationship to it; 4) substance-induced depression; or 5) depressive symptoms that are a normal response to being severely ill. These possibilities are considered under the two generic categories of mood disorders due to medical conditions and secondary depression.

34.2.2. Mood Disorders Due to Medical Conditions

34.2.2.1. Dementia of the Alzheimer's Type (DAT)

The frequency of depressive syndromes in patients diagnosed with DAT ranges from 17% to 31% (171). Treatment guidelines and limited clinical studies indicate patients should be considered for antidepressant therapy even if they do not meet criteria for a depressive syndrome (172, 173, 541, 542). The severity of dementia and the spectrum of depressive symptoms must be considered, as studies suggest that persistent affective symptoms, particularly in the early stages of dementia, are responsive to antidepressant therapy (174). Sertraline up to 150 mg/day (mean = 95 mg/day) was more effective than placebo in a 12-week study of patients with DAT and MDD. Mini-mental examination score was of $\geq$ 10 (mean = 15 to 16) in the patient population indicating the severity of the DAT to be in the mild to moderate range. Responders had better ratings on caregiver distress, activities of daily living and behavioral disturbances. This study suggests that the SSRI sertraline is probably effective in the treatment of depression in the presence of mild to moderate DAT. Apathy symptoms occurring later in the course of DAT probably do not respond to antidepressants, but may respond to stimulants although clinical intervention has not been documented by controlled studies.

34.2.2.2. Epilepsy

Endogenous depression was observed in 11% of outpatients with epilepsy; 30% of epileptics described previous suicide attempts (175). There have been no randomized controlled trials published in this population comparing any SSRI to other antidepressants or placebo. However, one 6-week RCT demonstrated that amitriptyline 75 mg/day and nomifensine 75 mg/day were more effective than placebo in the treatment of epileptic patients with major depression (176, 543). An issue of particular concern is the potential for drug-drug interactions. Careful screening of potential drug-drug, drug-food, and drug-disease interactions are imperative, as antidepressants and anticonvulsants are both classes of medications with a high potential for interacting with metabolism.

34.2.2.3. Multiple Sclerosis (MS)

Major depressive episodes are estimated to range between 40–70% of patients with MS (177). Fluvoxamine 200 mg/day for 3 months was effective in 79% of 43 interferon beta-1b treated patients affected by MDD associated with MS (178). A 5-week course of desipramine (125–200 ng/ml) was effective in ameliorating symptoms of major depression in 86% of patients with MS in contrast to only 43% of patients treated with placebo (179). Paroxetine and sertraline have also been studied and found to be beneficial (544–546).

34.2.2.4. Stroke

Eighteen percent of patients recovering from stroke experienced a major depression within two months of the occurrence (180). The effectiveness of antidepressant therapy of medications including nortriptyline to 100 mg/day, fluoxetine 20 mg/day, citalopram to 40 mg/day, and trazodone to 200 mg/day, in dysthymic and depressed post-stroke patients have been documented (181–185, 547). Therapeutic doses of fluoxetine or nortriptyline treatment improved survival (68%) versus placebo (38%) in a follow-up study for up to 9 years (186). The results of one study have suggested that a left sided stroke predicted SSRI treatment resistance and a higher incidence of MDD (187).

34.2.3. Secondary Depression with Medical Illness Disorders

34.2.3.1. Cancer

Symptoms of depression are common in patients with cancer. One report found that 42% of patients with cancer experienced major depression with 24% being judged severely depressed (188). The highest rates occurred in advanced cancer and in patients with greater degrees of discomfort and disability. An 8-week trial found the SSRI paroxetine (20–40 mg/day) and the TCA amitriptyline (75–150 mg/day) equally effective in the treatment of depression in women with breast cancer (189). While antidepressants appear to be effective in the treatment of depression in patients with cancer it is not clear which antidepressant or class of antidepressants is preferred (548).

34.2.3.2. Diabetes Mellitus

Depression is approximately three times more prevalent in patients with diabetes than in the general population. A small 10-week controlled trial did not find paroxetine more effective than placebo in the treatment of 15 mildly depressed women with non-optimally controlled type 2 diabetes (190). There was a trend for superior efficacy of paroxetine in clinician-rated anxiety and depression, however. A controlled trial of 60 insulin dependent diabetics with significant depressive symptoms and diabetic neuropathies found that a 10-week course of imipramine or amitriptyline 100 mg/day was effective in reversing both disorders (191). While SSRIs have been most studied and appear to be effective in the management of depression in patients with diabetes, it is not clear how they compare to other antidepressants or antidepressant classes (549). Duloxetine is FDA approved for the management of diabetic peripheral neuropathic pain.

34.2.3.3. Fibromyalgia

Fluoxetine has been found ineffective in one trial and effective in one trial of patients with fibromyalgia and depressive symptoms (192). The positive study, a 12-week, RCT found fluoxetine (10–80 mg/day) was more effective than placebo for reducing pain, fatigue and depression symptoms in 60 women with fibromyalgia, although scores for tender points and myalgia did not improve (193). Duloxetine 60 or 120 mg/day was more effective than placebo in reducing pain scores in women diagnosed with fibromyalgia with or without a concomitant diagnosis of major depression (194). A meta-analysis of nine RCT involving TCA suggested that the greatest improvement from the antidepressants was associated with sleep quality while only modest improvement was found in measures of stiffness and tenderness (192). Duloxetine is FDA approved for the management of fibromyalgia. Milnacipran, while not approved for the treatment of depression is a serotonin and norepinephrine reuptake inhibitor that is approved for the management of fibromyalgia.

34.2.3.4. HIV Seropositivity

An estimated 4–14% of HIV positive patients meet criteria for major depression. Fluoxetine was found more effective than placebo in the treatment of HIV positive patients diagnosed with either major depression or dysthymia (195). A 6-week controlled trial of imipramine (mean = 241 mg/day) was effective in 74% of trial completers while placebo was effective in only

26% (196). Neither study found a difference in the depression response rate between patients with more or less severe immunodeficiency. TCAs and SSRIs appear to be effective in treating depressive symptoms in patients with HIV infection. One needs to be mindful of the potential for drug-drug interactions when combining antidepressants with antiretrovirals (550, 551).

34.2.3.5. Myocardial Infarction (MI)

It is estimated that 45% of patients admitted for an MI will develop symptoms of major or minor depression within 8–10 days (197). Depression while hospitalized after an MI is a significant predictor of 18-month post-MI cardiac mortality, with the greatest risk among patients with greater than 9 premature ventricular contractions (PVC) per hour. This finding is compatible with the literature suggesting an arrhythmic mechanism as the link between psychological factors and sudden cardiac death. The relationship between depression and increased morbidity and mortality is well documented in post-myocardial infarction patients as well as in coronary artery disease patients without myocardial infarction. Therefore, clinicians are advised to treat major depression when present in this patient population (198). TCA are contraindicated in the first 6 weeks following a myocardial infarction, due to their cardiovascular-related ADR profile (199). A RCT contrasting the effectiveness of fluoxetine to placebo among patients 3 months post MI who were also diagnosed with major depressive disorder failed to show a difference between the two treatments (200). A case-control study involving nearly 8700 patients exposed to antidepressants following an acute MI concluded recent past use of SSRI is associated with a slightly decreased risk for acute MI compared with non-use of SSRI. This is postulated to be a result of anti-platelet effects of the drugs (201).

While SSRIs appear to be safe and effective for the management of depression in post-MI patients their benefit has been challenged (552, 553).

34.2.3.6. Post-partum Depression

Post-partum depression affects approximately 10% to 15% of childbearing women (202). Prophylactic nortriptyline to 75 mg/day was successful in preventing depression recurrence in post-partum patients with a previous history of post-partum illness (202). Untreated patients were found to experience a 63% recurrence rate while only a 7% rate was found in the treated patients. Fluoxetine was significantly more effective than placebo following an initial session of counseling. The effect was as effective as a full course of cognitive-behavioral counseling in the treatment of postnatal depression. There was no interaction between medication and counseling (203). Treatment of post-partum depression with a SSRI requires one to consider the fetal and neonatal effects of SSRI exposure (554).

34.2.4. Dysphoria with Schizophrenia

Studies consistently demonstrate that the addition of a SSRI or a TCA to the medication regimen of a chronic schizophrenic has no positive effects over antipsychotic treatment alone, and in some instances, may worsen thought disorder (204–208). Thus it is recommended that patients relapsing with psychotic symptoms including depressed mood be treated with an increase in their antipsychotic dose rather than adding an antidepressant to a subtherapeutic antipsychotic dose. However, in the event of emergence of postpsychotic depression or increased frequency of negative symptoms, addition of an antidepressant to the antipsychotic agent, is an important and useful adjunct as shown by multiple positive studies (209).

34.2.5. Dosing

The dosage usually recommended for fluoxetine is 20–80 mg daily. Fluoxetine is usually initiated at 20 mg/day; however, lower starting doses have been used for patients with comorbid anxiety symptoms. A fixed dose study comparing fluoxetine 20 mg, 40 mg, and 60 mg to placebo showed no significant differences in the response rates of the three doses of fluoxetine (210). A therapeutic trial of fluoxetine is considered to be 4–6 weeks. The usual dose of paroxetine for depression is 20 mg to 50 mg daily. This medication can be taken at bedtime since it is considered the most likely of the SSRI to cause sedation. The initial starting dose is 20 mg daily for 2–3 weeks and can be titrated weekly in increments of 10 mg. A comparison study found equivalent efficacy with mean doses of 31 mg daily of paroxetine and 42 mg daily of fluoxetine (211). The usual recommended antidepressant dose for sertraline is 50–200 mg daily. The medication may be taken either in the morning or evening in one dose. The initial dose is usually 50 mg daily for 2–3 weeks and may be titrated by 50 mg weekly. Direct comparison between sertraline and fluoxetine showed equivalent doses of 72 mg/day for sertraline and 28 mg/day fluoxetine (212). The usual recommended antidepressant dose for fluvoxamine (though not indicated for depression) is 50–300 mg daily. Doses over 150 mg daily should be split in two doses. Daytime doses may be taken with food to minimize gastrointestinal ADR. The usual recommended

TABLE 34.3 Adult dosages for US available antidepressants.

Generic name	Trade name	Initial dose (mg/day)	Usual dose range (mg/day)
Selective serotonin reuptake inhibitors			
Citalopram	Celexa	20	10–40
Escitalopram	Lexapro	10	10–20
Fluoxetine	Prozac	10–20	20–80
Fluvoxamine	Luvox	50	100–300
Paroxetine	Paxil	20	20–50
Sertraline	Zoloft	50	50–200
Vilazodone	Viibryd	10	10–40
Serotonin/norepinephrine reuptake inhibitors			
Duloxetine	Cymbalta	20	40–60*
Desvenlafaxine	Pristiq	50	50–100
Levomilnacipran	Fetzima	20	40–120
Venlafaxine	Effexor	75	75–375
Serotonin 5HT2 receptor antagonists			
Nefazodone	Serzone	200	300–600
Trazodone	n/a	150	150–600
Serotonin 5HT3 receptor antagonist			
Vortioxetine	Brintellix	10	5–20
Serotonin/norepinephrine reuptake inhibitors (Tricyclic)			
Amitriptyline	Elavil	50	50–300
Amoxapine	Asendin	100	100–400
Clomipramine	Anafranil	75	75–250
Desipramine	Norpramin	75	75–300
Doxepin	Sinequan	75	75–300
Imipramine	Tofranil	50	50–300
Nortriptyline	Pamelor	50*	50–150*
Protriptyline	Vivactil	15	15–60
Trimipramine	Surmontil	50	50–300
Serotonin/norepinephrine reuptake inhibitors (Tetracyclic)			
Maprotiline	Ludiomil	75	75–300
Dopamine/norepinephrine reuptake inhibitor			
Bupropion	Wellbutrin	150*	300–450
Norepinephrine autoreceptor antagonist and 5HT1A specific serotonin agonist			
Mirtazapine	Remeron	15	15–45
Monoamine oxidase reuptake inhibitors			
Isocarboxazid	Marplan	20	20–60
Phenelzine	Nardil	15	15–90 or 1 mg/kg/day
Selegiline Patch	Emsam	6 mg/24 hour	6–12 mg/24 hour
Tranylcypromine	Parnate	20 mg*	20–60 or 0.7 mg/day*
Melatonin agonist/5HT2C antagonist			
Agomelatine	Valdoxan	25	25–50

*Dose changes made by the editor.

dose of citalopram is 20–40 mg daily for individuals less than 60 years of age. Initial dosing is usually 20 mg daily for one week. Doses greater than 40 mg daily are not recommended due to the risk of QT prolongation. Escitalopram 10–20 mg daily was found to be as effective as citalopram 40 mg daily in a fixed dose trial (213). A summary of the usually recommended doses of the antidepressants is presented in Table 34.3.

34.2.6. Adverse Effects

The SSRI ADR profile differs considerably from that of the TCA and MAOI. Anticholinergic ADR, orthostatic hypotension, and weight gain are not usually observed as frequently as with the latter agents. There are differences in frequency of reporting of ADR between individual SSRIs.

34.2.6.1. Cardiovascular

The SSRI do not affect blood pressure, but may cause slight decreases in heart rate. Except for citalopram, there are no data to expect that SSRIs are cardiotoxic; and arrhythmias following overdose are quite rare. A pharmacoepidemiologic study of 6,291 person years follow-up of SSRI users showed no increased risk of sudden cardiac death of SSRI users versus persons not using antidepressants (214).

34.2.6.2. Central Nervous System

Anxiety/agitation, tremor, and insomnia associated with SSRIs are symptoms thought to be a hyperstimulation or akathisia-like reaction. This usually lasts approximately one month (215). Approximately 10–25% of fluoxetine treated patients may experience this ADR. Slow upward dose titration, dose reduction, or other pharmacological interventions may be useful. Serotonin syndrome (SS), a potentially fatal precipitous increase in CNS concentrations of serotonin, has been reported when multiple serotonergic agents are used concomitantly including MAOI. Presenting symptoms of SS may include autonomic symptoms such as tachycardia, diaphoresis, labile blood pressure, shivering, tachypnea, mydriasis, and sialorrhea; mental status changes such as dysphoria, hypomania, irritability, anxiety, confusion, delirium, and coma; neurological symptoms include tremor, myoclonus, hyperreflexia, ankle clonus, muscle rigidity, ataxia, and incoordination; gastrointestinal symptoms such as nausea, vomiting, diarrhea, and disseminated intravascular coagulation. Hyperthermia is associated with potential lethality. MAOI should be discontinued for at least two weeks prior to initiating therapy with another serotonergic antidepressant, and five half-lives of serotonergic drugs (and their active metabolites) should pass prior to initiating a MAOI. Sexual dysfunction has been reported at varying rates. Sexual ADR include ejaculatory incompetence, ejaculatory retardation, anorgasmia, inability to obtain or maintain an erection, or decreased libido. Prevalence rates vary, but the rates would not be expected to differ greatly among the different SSRIs. In reports inquiring about patients' sexual function, the incidence of sexual dysfunction ranged from 34–75% (216, 217). Suicidal ideation among adults has been associated with fluoxetine in case reports (218), however subsequent meta-analysis of fluoxetine efficacy trials in adults failed to show either an increased risk of suicidal acts or ideation for either fluoxetine or the other comparator versus placebo (219). Reports of increased suicidal risk associated with SSRI usage in adults have also been discounted by a survey of 48,277 patients participating in FDA registration of antidepressant studies, which showed the rates of suicide were similar between the SSRI, comparator antidepressants and placebo (220). However, later a boxed warning was added to the antidepressants prescribing information. The FDA warned prescribers that SSRI used in children and adolescents may double the risk of suicidal ideation from 2% placebo to 4% for SSRI and other second-generation antidepressants (221). The FDA report has been strongly challenged by a study of over 24,000 adolescents diagnosed with MDD, which concluded that antidepressant use had no effect on the likelihood of suicide attempts (222).

When SSRIs are to be discontinued, tapering should occur over 1–2 weeks to avoid withdrawal symptoms, with the exception of fluoxetine. Patients discontinuing paroxetine, fluvoxamine, sertraline, and fluoxetine experienced withdrawal reactions, including at respective rates of 14, 20, 2.2 and 0% (223). Criteria for SSRI withdrawal include two or more of the following symptoms within one to seven days following discontinuation of a month or more of SSRI treatment: dizziness, light-headedness, vertigo, paresthesias, anxiety, diarrhea, fatigue, gait instability, headache, insomnia, irritability, nausea, tremor, visual disturbances (224).

Like the TCAs, the SSRIs can cause "switching" of patients symptoms from depression to hypomania/mania most commonly in patients with bipolar illness.

34.2.6.3. Gastrointestinal

The nausea associated with SSRIs is generally mild, transient, rarely associated with vomiting, and more prevalent with SSRIs than TCAs. Fluoxetine-treated patients may experience a weight loss proportional to their body weight at the start of therapy. Sertraline, unlike fluoxetine, is equally likely to cause weight gain as weight loss in patients (225). Use of paroxetine for greater than 6 weeks is associated with weight gain in 9% of patients (226, 555). Fluvoxamine was found to cause weight loss in non-vomiting eating disorder patients (227).

34.2.6.4. Hematologic

Serotonin potentiates platelet activation. SSRIs decrease serotonin uptake from blood to platelets. Since platelets do not synthesize serotonin, SSRIs are associated with increases in bleeding episodes. This is particularly true if used concomitantly with aspirin, NSAIDs, warfarin or other anticoagulants. Similar bleeding risk was not associated with nortriptyline, protriptyline, desipramine, trimipramine, maprotiline, and amoxapine.

34.2.6.5. Renal

All SSRIs are associated with drug-induced syndrome of inappropriate Antidiuretic Hormone Secretion (SIADH). SIADH presents with symptoms that may include confusion, lethargy, dizziness, fatigue, anorexia and delirium (228). Symptom onset is within 3 days to 4 months of the start of treatment with the majority of the cases occurring in the elderly. Geriatric patients receiving fluoxetine should be monitored for electrolytes changes weekly during the first month of treatment.

34.2.7. Third Generation Antidepressants (TGAD)

34.2.7.1. Indications

These agents consist of amoxapine, bupropion, duloxetine, maprotiline, mirtazapine, trazodone, venlafaxine, desvenlafaxine, vilazodone, nefazodone, levomilnacipran, and vortioxetine. All agents are FDA-approved for the treatment of MDD. Amoxapine is also approved for MDD with psychotic features, bupropion is approved for seasonal affective disorder and smoking cessation, venlafaxine is approved for generalized anxiety disorder, social anxiety disorder, and panic disorder and duloxetine is approved for generalized anxiety disorder, diabetic peripheral neuropathic pain, fibromyalgia, and chronic musculoskeletal pain.

34.2.7.2. Efficacy

The overall response for a meta-analysis of antidepressant efficacy including amoxapine, bupropion, maprotiline, and trazodone were 55% for inpatients with MDD and 62% for outpatients with MDD. These rates are similar to TCA, MAOI and SSRI response rates (143). TGAD are alternative agents for patients failing an initial course of TCA.

A meta-analysis of SSRIs compared to venlafaxine trials suggested that venlafaxine was associated with a 7% higher remission rate (229). This finding was not observed between venlafaxine and the TCAs and mirtazapine. Duloxetine is an agent similar in mechanism of action to venlafaxine. The studies of duloxetine found the drug to be as effective or more effective than the comparator SSRI, paroxetine, and more effective than placebo although three failed trials were associated with the drug. Bupropion was effective in 63% of TCA-refractory patients (230). Trazodone was effective in 45% (10/22) of treatment refractory depressed patients in a four-week trial (231). A four-week trial of amoxapine was as effective as an amitriptyline/perphenazine combination in treating MDD with psychotic features (232). The combination showed slightly better global ratings, but a greater incidence of EPS. Like all other antidepressants, TGAD are effective in preventing relapses of depression. Bupropion was equal to amitriptyline in a 6–12 month follow-up study (233). Maprotiline 75 mg/day administered prophylactically to 1141 patients for one year, resulted in a 16% relapse rate in contrast to a 32 to 38% relapse rate for patients treated with placebo (234).

34.2.7.3. Dosage

Amoxapine may be initiated at 150 mg/day and increased in 25 to 40 mg daily increments to the recommended dose of 200–300 mg/day, given as a single dose at bedtime. Elderly patients should be started on an initial dose of 75 mg/day (235). There has been a questionable finding that amoxapine may have a faster onset of action than the TCAs, and also have been some reports of a premature loss of efficacy after 6–12 weeks of therapy in some patients (235).

Bupropion is available as three different formulations. The immediate release formulation is initiated at 100 mg twice daily. Dose increases should not exceed more than 100 mg/day in a 3-day period. The maximum dose should not exceed 450 mg/day. Doses should be taken 4 to 6 hours apart to minimize the risk of seizures. The sustained release dosage formulation is instituted at 150 mg q AM and then increased to 150 mg twice daily at day-4. Eight hours should be allowed between doses. The maximum recommended sustained release dose is 200 mg twice daily (236). The extended release formulation is given as one single daily dose. Initiation dose is 150 mg/day, to be increased to 300 mg/day not before day-4. If several weeks of treatment elapse without response, a dose increase to 450 mg/day may be considered. To avoid insomnia complaints, clinicians often instruct patients to take the last dose of the immediate release or sustained release formulations during the day not later than 6 hours prior to bedtime, and the extended release formulation is given as a once-daily dose in the morning.

Duloxetine is given at a total daily dose ranging from 40–60 mg/day given once daily without regard to meals. There is no evidence that doses greater than 60 mg/day are more effective than smaller doses. The dose does not need to be adjusted for age, gender, or smoking. There is no evidence that doses greater than 60 mg/day are more effective than 40–60 mg/day (50).

The dose recommendations for maprotiline (3 to 5 mg/kg) are identical to those of imipramine, amitriptyline, and desipramine. A daily dose of 150 mg is considered the threshold level for treating acute depressions, and 300 mg/day is considered the maximum dose. It can be given once daily, preferably at bedtime. It is recommended that the initial dosage and titration in the elderly should be conservative, as hallucinations have been reported in that population at doses of 200 mg (237). Claims that maprotiline, like amoxapine, has a more rapid onset of action than the TCAs is inconsistently supported with the available data (237).

Mirtazapine is initiated at 15 mg daily, given as one dose at bedtime. Patients may then be increased to 30 mg and then increased to 45 mg if needed at intervals of 1 to 2 weeks (236). At dose greater than 45 mg/day, the sedating properties of the drug are blunted out by increased norepinephrine agonist activity at higher doses.

The initial dose of trazodone is 150 mg/day. Trazodone may be increased to a maximum inpatient dose of 600 mg/day at a rate of 50 mg/day every third day. Many of the patients who are nonresponsive to trazodone are unable to tolerate the drug's sedation, thereby leading to the prescribing of subtherapeutic doses. Despite the drug's short half-life, it is preferable to give the entire dose at bedtime to take advantage of the strong sedative action of the drug (238).

Nefazodone is dosed 200 mg per day in two divided doses. The usual dose range is 300 to 600 mg per day in two divided doses.

Venlafaxine is available as an immediate release or an extended release formulation. The initial dose of venlafaxine immediate release is 75 mg/day, administered with food. This dose may be increased to 150 mg/day, depending on efficacy and tolerability. Titration should be undertaken at increments of no more than 75 mg/day and at no less than 4-day intervals. In severely depressed or hospitalized patients, the recommended starting dose is 75–150 mg/day, which may then be increased further over the next 7 days. The minimum effective dose of venlafaxine is 75 mg/day with a maximum dose of 375 mg/day administered in 2 or 3 divided doses. Doses of 300 to 375 mg/day were associated with the most treatment-emergent adverse events, discontinuations, and largest changes in blood pressure in clinical trials. Therefore, the usual dosage range is 75–225 mg/day, which appears to be adequate for most patients (239). The recommended starting dose for the extended release formulation is 75 mg/day administered with food as a single dose either in the morning or the evening. Dose increases should proceed at a rate of 75 mg/day at intervals of at least 4 days. Because of the risk of withdrawal reaction, it is recommended to taper patients off venlafaxine over a 7 to 14 days period (236).

Desvenlafaxine, the metabolite of venlafaxine, is dosed 50 mg daily. Doses up to 400 mg once daily have been studied but the manufacturer states that doses above 50 mg per day do not offer additional benefit.

The initial dose for vilazodone is 10 mg once daily for 7 days. It can then be increased to 20 mg once daily for an additional 7 days. The maximum recommended dose is 40 mg once daily.

Levomilnacipran is dosed 20 mg daily for 2 days, then increased to 40 mg once daily. It may be further increased in increments of 40 mg at 2 or more day intervals. The maintenance dose is 40–120 mg/day. Maximum dose is 120 mg/day.

The initial dose for vortioxetine is 10 mg once daily with an increase to 20 mg once daily as tolerated. Maintenance dose is 5–20 mg once daily. Note that dosage adjustments are required for patients who are CYP2D6 poor metabolizers as well as patients receiving CYP2D6 inhibitors (fluoxetine, paroxetine). In these situations the recommended maximum dose is 10 mg once daily. Also note that if patients are concomitantly receiving CYP inducers (carbamazepine, phenytoin, rifampin) that the maximum dose should not exceed three times the original dose.

A summary of the usually recommended doses of the antidepressants is presented in Table 34.2.

34.2.7.4. Adverse Effects

34.2.7.4.1. Amoxapine

The anticholinergic ADR of dry mouth, constipation, blurred vision, and urinary retention are the most common ADR reported for amoxapine. The incidence is similar to amitriptyline and imipramine, as are the incidence of orthostatic drops in blood pressure and sedation. Atrial flutter and fibrillation and conduction defects similar to those associated with the TCAs have been reported. Seizures have been reported at therapeutic doses of amoxapine. In overdoses, the drug seems to have the ability to produce unusual neurologic alterations, and may produce severe and frequent, i.e., 36%, generalized seizures or status epilepticus, associated with 15% fatality in overdose. Extrapyramidal side effects (EPS) may occur secondary to the dopamine blocking metabolite of amoxapine. Maintenance therapy with this agent is discouraged. Hyperprolactinemia can result in delayed menses, breast engorgement, loss of libido, galactorrhea, and fluid retention (65).

34.2.7.4.2. Bupropion

In contrast to amitriptyline, ADR that occur more often with bupropion include headache, decreased appetite, nausea, vomiting, agitation, insomnia, and decreased libido. Maculopapular lesions and/or pruritis occur at doses of 300–900 mg/day. The macu-

lopapular rashes clear in 3–4 days following drug discontinuation. Pruritis alone usually will clear with a reduction in dosage. A transient weight loss of at least 5 lbs has been found to occur over a 3–6 week treatment period in up to 30% of patients on bupropion. The weight returns to baseline within 6 months. The relationship between seizure occurrence and bupropion use at therapeutic doses is 0.87%. The incidence is 0.44% in patients receiving doses no greater than 450 mg/day while the rate for doses greater than 450 mg/day demonstrated a five-fold increase, to 2.2% . Seizure risk factors included a history of bulimia, doses greater than 450 mg/day and a past history of seizures. Because bupropion has dopamine agonist activity, it is questionable whether to utilize the drug in the treatment of delusion or hallucinating patients (65). Although the drug has been used in schizophrenic patient as a smoking cessation treatment (240), nicotine replacement is indicated before bupropion treatment.

34.2.7.4.3. Duloxetine

The most commonly reported ADR is nausea, which is dose-dependent and may occur in up to 28% of patients. This effect is reported to last approximately one week. Other adverse events reported include diarrhea, and fatigue. Diastolic blood pressure in 9-week trials was reported to increase an average of 2 mm Hg. Pulse increases averaging 2 bpm were reported in studies up to 13 weeks. Duloxetine, like most antidepressants, is associated with sexual dysfunction in men (65).

34.2.7.4.4. Maprotiline

Since this antidepressant is a molecular manipulation of the TCA, it is not surprising that its ADR profile is similar to the TCAs with a few notable exceptions. The anticholinergic ADR occur with similar frequencies for maprotiline when compared with amitriptyline and imipramine. ECG abnormalities are similar to those seen with amitriptyline. Postural hypotension is less common with maprotiline than with amitriptyline. Rashes occur twice as frequently with maprotiline than with amitriptyline or imipramine. They are described as usually small, localized, and non-pruritic. Of the less common effects, maprotiline-induced seizures have received the most attention. The prevalence of seizures in patients receiving maprotiline was observed to be 16% versus 2% in TCA-treated patients (65).

34.2.7.4.5. Mirtazapine

Mirtazapine was associated with dry mouth, drowsiness, excessive sedation, increased appetite, and weight gain more frequently than placebo in clinical trials. As compared to amitriptyline, mirtazapine was associated with less dry mouth, constipation, tremor, vertigo, tachycardia, and abnormal vision. The incidence of neutropenia associated with mirtazapine was 0.062 for mirtazapine versus 0.045 for amitriptyline versus 0.014 for placebo. Two cases of agranulocytosis occurred in clinical trials. Liver function test abnormalities may occur at a rate 1.4 times higher than other antidepressants and 1.6 times higher than placebo. Nonfasting cholesterol and triglyceride levels increased in controlled trials by 20% (65).

34.2.7.4.6. Trazodone

The most common ADR with trazodone is sedation. Anticholinergic ADR are not associated with trazodone. Initially trazodone was considered to be a non-cardiotoxic drug because it did not increase ventricular conduction. However, it has been shown to exacerbate preexisting myocardial irritability, which potentially has resulted in ventricular tachycardia. Patients with cardiac arrhythmias and/or mitral valve prolapse should be carefully monitored when administered trazodone. Orthostatic hypotension differs from the TCAs in that it is transient and only lasts for approximately four to six hours after the dose. The problem can be avoided by administering the drug at bedtime. It can also cause bradycardia. Drowsiness is the most commonly reported ADR and has been reported in up to 45% of patients. There are reports of hepatoxicity within the first few weeks of trazodone therapy that are reversible after drug discontinuation. A total of 123 cases of trazodone-associated priapism have been reported in the United States to the manufacturer, who estimates the incidence at a conservative one in 6,000 male patients due to the voluntary reporting nature of the system (65).

34.2.7.4.7. Venlafaxine

Venlafaxine has a low occurrence of serious, rare adverse reactions. Most commonly reported adverse events include nausea and vomiting, at 37% and 6%, respectively. Many potential adverse reactions are dose related, including chills, hypertension, anorexia, nausea, agitation, dizziness, somnolence, tremor, yawning, sweating, and abnormal ejaculation. Serious events, described as rate per 100 patient-years of exposure, as compared to comparator antidepressants, are: seizure (0.4 versus 1.5), severe rash (0.8 versus 2.3), mania or hypomania (0.4 versus 0.0), death (0.4 versus 3.1), suicide (0.4 versus 0.8), suicide attempts (4.0 versus 3.1), suicidal ideation (0.4 versus 0.8), and significant elevations in liver function tests (0.8 versus 3.1) (65).

34.2.7.4.8. Vilazodone

The most common adverse reactions associated with vilazodone are nausea and diarrhea. Other common side effects include dizziness, insomnia, dry mouth, and decreased libido.

34.2.7.4.9. Levomilnacipran

Levomilnacipran is associated with dose dependent orthostatic hypotension and nausea. Other common side effects include tachycardia, hyperhidrosis, constipation, and dose related erectile dysfunction and urinary hesitancy.

34.2.7.5. Vortioxetine

Vortioxetine is commonly associated with sexual dysfunction and dose dependent nausea. Other common side effects include dizziness, diarrhea, dry mouth, constipation and vomiting.

34.2.8. Tricyclic Antidepressants

34.2.8.1. Efficacy

Patients with major depressive disorders with symptoms that include an insidious onset, anorexia, weight loss, middle or terminal insomnia, diurnal variation in mood, psychomotor retardation or agitation are more likely to experience a positive response to a TCA (241). In controlled studies in which the TCAs were compared with each other, it is consistently observed that overall no single TCA is superior to any other (242). Thus the choice of the TCA to be utilized is dependent upon the drugs' ADR profiles, the probability of response to an individual TCA, based on blood levels, and the patient's past response to a particular agent.

34.2.8.2. Indications

34.2.8.2.1. Major Depressive Episode

TCA efficacy in the treatment of acute depressions is well established. A 1965 review calculated the imipramine response rates in controlled studies to be 65% compared to 32% in placebo-treated patients, a figure that has remained stable across studies and time (243). A 66% initial response rate for antidepressant drug treatment was calculated for a series of studies published between 1974 and 1985 (244). A meta-analysis of antidepressant efficacy studies found the TCA response rate to be 51%, 21% to 25% better than the placebo response rate (143). One third to one half of patients with major depression will not respond to TCAs, however, the management of these treatment resistant patients is an appropriate question. ECT was estimated to be effective in 72% of TCA treatment failures (245). The augmentation of TCA therapy with lithium has been shown to be effective in 63% of treated patients versus a 12% rate in controls (65). Some patients respond quickly, relapse within a few days, and then respond with continued lithium treatment. Most responders will do so within 21 days. Usually, lithium doses of 600–1200 mg/day producing concentrations in excess of 0.3 mEq/L are sufficient.

34.2.8.2.2. Major Depressive Episode with Psychotic Features

Depressed patients who are delusional normally require ECT. The literature estimates that 82% of patients who fail to respond to TCAs will respond to ECT (246). While 66% of nondelusional, depressed patients respond to TCAs, only 34% of delusional depressed patients respond to a three-week trial of TCAs. If ECT is not a viable alternative, the possibly less effective combination treatment of a TCA with an antipsychotic may be recommended. Combination drug treatment can be optimized by prescribing a TCA dose that falls within the higher end of the recommended therapeutic plasma ranges for the TCA. As an example, a nortriptyline concentration of 140–150 ng/ml would be a reasonable initial target concentration. If the patient does not respond, higher doses may be utilized. Antipsychotic drugs interact with TCAs to increase their concentrations. Thus, it is hypothesized that the ineffectiveness of TCAs in treating delusional depression may be the result of utilizing subtherapeutic doses. Only 41% of delusional depressives treated with amitriptyline responded whereas the antipsychotic/antidepressant combination of perphenazine/amitriptyline was, as expected, effective in 78% of patients (247). However, after the data considered the effect of the drug's serum concentration, it was found that the 64% of the amitriptyline patients with total levels greater than 250 ng/ml responded, which was a similar response produced by the combination drug treatment of a TCA and an antipsy-

chotic. Even more important than the TCA dosage is the duration of TCA treatment. A 9-week trial of primarily amitriptyline or imipramine (200–250 mg/day) in delusional depressives resulted in response rates of only 32% after three weeks but 62% after 9 weeks (248). Thus, TCA is effective in the treatment of delusional depression, but probably only at high therapeutic blood levels given for up to nine weeks.

34.2.8.2.3. Continuation and Maintenance Treatment

Between 50% and 85% of patients with major depression will experience at least one additional episode in their lifetime. Nearly 50% of these patients will relapse within two years, with the greatest risk of relapse occurring within four to six months of the initial remission. Finally, 15% to 20% of patients with recurrent depression do not fully recover from any given episode (249). The greatest risk for relapse occurs in the 4–6 months of the initial remission. Relapse rates in TCA trials of continuation therapy in relapse prevention ranged from 0 to 32% for TCA versus 31 to 73% for placebo (250, 251) and relapse rates in controlled trials of TCA maintenance therapy reported results of recurrent major depression in 15 to 54% of TCA versus 52% to 63% for placebo (252, 253).

34.2.8.3. Dosing

34.2.8.3.1. Empirical Dosing

When empirically dosing patients with TCAs imipramine and amitriptyline, treatment with either drug is initiated at a dose of 25, 50, or 75 mg/day administered as a single dose at bedtime because of the TCA long half-lives. The dose should then be increased by 25–50 mg every one to two days until a dosage of 150 mg/day is reached. If a response is going to occur, the patient should show significant clinical improvement in anxiety, physical expression of distress, cognitive impairment and depressed mood within the first week at this dose. If these symptoms have not improved and if there are no medical contraindications or manifestations of toxicity, the dosage should be titrated upward at a rate of 25 mg/day, normally to a maximum dose of 300 mg/day or until the patient begins to demonstrate improvement or intolerable side effects occur. This dosing schedule is appropriate not only for imipramine and amitriptyline, but also for doxepin, desipramine, and trimipramine. However, the dose must be adjusted downward for nortriptyline, which is approximately two times more potent than imipramine, and protriptyline, which is five times more potent than imipramine. A summary of the usually recommended antidepressant doses is presented in Table 34.3.

34.2.8.3.2. Therapeutic Trial

Commonly, four weeks of therapy are required before improvement in mood and affect become apparent to the physician, the family, and the patient. This delay must be explained to patients and their families to increase compliance. If there is no response by week four, the medication should be changed; however, if a partial response or improvement has been noted, the patient should continue the trial until week six (254). Of non-delusional depressed patients who respond to TCA, it has been reported that 88% do so within three weeks, whereas a similar percentage, 90%, of delusional depressives require up to 7 weeks to respond (248).

The acutely depressed patient must remain on the TCA until asymptomatic for at least 16 weeks. Without this, the patient will have a 50% risk of experiencing a relapse within the next 4–6 months following the initial remission (249). When discontinuing therapy in the outpatient setting the TCA should be tapered at the rate of approximately 50 mg per week for amitriptyline, imipramine, desipramine, doxepin, and trimipramine; 25 mg per week for nortriptyline; and 10 mg per week for protriptyline. Inpatients can be tapered at a faster rate (every third day) since they are being monitored on a daily basis. If the TCA is abruptly discontinued, a withdrawal syndrome including nausea, headache, malaise, vomiting, dizziness, chills, cold sweats, abdominal cramps, diarrhea, insomnia, anxiety, restlessness, and irritability can occur. If the immediate discontinuation of a TCA is imperative and the patient subsequently experiences TCA withdrawal symptoms, the administration of an anticholinergic medication such as diphenhydramine will usually reverse the symptoms (65).

34.2.8.3.3. Blood Levels

A review of the studies examining the relationship between the antidepressant effect of TCAs and their plasma concentrations concluded that imipramine, nortriptyline, and desipramine blood level measurements generate information that can increase patient response rates (255). Desipramine data was found to produce the strongest evidence of a therapeutic threshold. The desipramine response rate above the therapeutic response threshold (≥116 ng/ml) was 51%, compared with only 15% below the threshold. For nortriptyline, the therapeutic window of 58–148 ng/ml demonstrated a 66% response rate within the range

whereas the response rate outside the "window" was only 26%. A therapeutic window for imipramine (imipramine and desipramine) ranges from 175 to 350 ng/ml. The likelihood of response to imipramine was 67% within the therapeutic window to 39% outside the window. For the remaining TCAs there is not enough data available in the literature to come to any firm conclusion as to the validity of plasma concentration measurements. Since absorption and tissue distribution of a TCA may take as long as five to eight hours, it is recommended that steady-state plasma sampling be carried out at approximately 12 hours after the last dose. A 12-hour sampling time guarantees that plasma levels are being measured during elimination phase of the tricyclic, which in contrast to the absorption and distribution phase demonstrates much less flux in the levels. The plasma sample should be drawn after steady state (when the amount of drug ingested daily equals the amount of drug excreted daily) has been reached (usually one week).

34.2.8.3.4. Retrospective Dosing

Since TCAs follow first-order linear kinetics, as the dose increases or decreases, the steady state TCA concentration must increase or decrease proportionately. Thus, a patient with a steady state nortriptyline concentration of 50 ng/ml at 75 mg/day, will have a steady state level of 100 ng/ml if the dose is increased to 150 mg/day, whereas if the dose is decreased to 50 mg/day, the steady state level should be 33 ng/ml. It must be remembered that the steady state TCA level in this mathematical relationship is the mean plasma concentration not the peak or 12-hour or trough plasma level. However, clinically this method can be utilized as a reasonable approximation of the 12-hour steady state level (256).

34.2.8.4. Adverse Effects

From a practical standpoint, the TCAs are classified as either dimethylated, or tertiary amine, TCAs, (amitriptyline, imipramine, doxepin, and trimipramine) or monomethylated, secondary amine, TCAs (nortriptyline, desipramine, and protriptyline). The dimethylated amine TCAs primarily block serotonin reuptake, while the monomethylated amine TCAs primarily block norepinephrine reuptake. Dimethylated TCAs are clinically considered to be more sedating, more potent as anticholinergic agents, and cause greater weight gain than the monomethylated TCAs. Monomethylated TCAs cause less postural hypotension than does the dimethylated class (257).

34.2.8.4.1. Anticholinergic Effects

Anticholinergic adverse effects are not necessarily dose related and usually mild and remit after a few weeks. Blurred vision noticed when the patient focuses on close objects, is rarely serious and usually lasts about one week. Dose reduction may be helpful if the problem is persistent or serious. Patients should be cautioned against operating motor vehicles if the problem is marked. Urinary retention is most commonly manifested as urination difficulty or hesitancy because of the increase in bladder sphincter tone and volume of fluid necessary to trigger detrusor contraction. It is related to dose, patient age, and duration of treatment. It may be helped by bethanechol. The prevalence of dry mouth is 60% of the depressed patients taking imipramine, although 20% of patients treated with placebo also complained of this ADR. TCA-induced constipation occurs in 15% of patients. It is best treated with a bulk laxative such as Metamucil, hydration, and/or exercise. TCAs can increase intraocular pressure in patients with closed-angle but not open-angle glaucoma. An in vitro estimation of the anticholinergic potency of the TCAs that considered the potency of the individual agents yielded the following order of anticholinergic activity: amitriptyline > trimipramine > doxepin > imipramine > protriptyline > desipramine > nortriptyline. If anticholinergic ADR are perceived either prospectively or retrospectively as a problem, the use of a less anticholinergic TCA such as desipramine or nortriptyline may be helpful (65).

34.2.8.4.2. Cardiovascular

The most common cardiovascular problem precipitated by TCA use is orthostatic hypotension. The problem can be minimized by utilizing nortriptyline. Among patients with first-degree atrioventricular (AV) block, there has been found to be a small risk of progressive block. If TCAs are used, ECG and TCA concentration monitoring are necessary. Patients with bundle-branch blocks have 10 times increased risk of developing a 2:1 AV block as compared to patients with normal ECG. In this situation, it may be beneficial to use an SSRI or bupropion in ischemic heart disease patients with mild to moderate depression, and not consider a TCA until the patient fails to respond to other options. Nortriptyline, or ECT, however, has been preferred in patients with severe, melancholic depression and cardiovascular disease, a recommendation based on risk-benefits ratios of probable increased mortality risk versus the efficacy of the TCA (258). The TCA do not cause any further impairment of the left ventricular ejection fraction in patients with congestive heart failure. However, imipramine but not nortriptyline does cause a worsening

of orthostatic hypotension. TCA-induced sinus tachycardia (rate > 100/min) is uncommon at therapeutic doses and symptomatic sinus tachycardia is rare. Should the latter occur, a less anticholinergic TCA such as nortriptyline is indicated. In patients with prolonged PR intervals, TCA are not contraindicated. However, these patients require ECG monitoring until maximal TCA doses are reached. Patients having bundle branch blocks require blood pressure, TCA plasma concentration, and ECG monitoring. Therefore, ECT or other antidepressants are more appropriate treatment alternatives. In patients with ventricular arrhythmias, premature ventricular contractions decrease significantly when receiving TCA, due to quinidine-like antiarrhythmic effects of TCA. This issue must be considered when patients are taking a Type 1 antiarrhythmic, as the dosage may need to be changed. Patients receiving antiarrhythmics will require close ECG monitoring (65).

34.2.8.4.3. Dermatologic

Cutaneous vasculitis, urticaria, and photosensitivity are the dermatological ADR that have been reported. Usually occurring within the first two months of therapy, the skin reactions usually are harmless and rarely require discontinuation of therapy (65).

34.2.8.4.4. Hematologic

Hematological ADR secondary to the TCA are usually neither a serious nor a common problem. Eosinophilia can occur in the first few weeks of therapy. Leukopenia is also an apparently benign and transient effect of the TCA. Agranulocytosis, although quite rare, has a 10–20% mortality rate. It occurs most often in the second month of therapy, usually in elderly, female patients. Routine periodic white blood cell counts are not recommended (65).

34.2.8.4.5. Hepatic

Jaundice associated with cholestasis has been described with the TCA. Elevations of transaminases and alkaline phosphatase are common during TCA treatment; however, the liver may not necessarily be the origin of the enzyme elevations. If increases are noted, the liver-specific enzyme, gamma-glutamyltranspeptidase (GGT) should be measured. Discontinuation is usually only indicated if the patients become symptomatic. Patients should become cognizant of the symptoms of jaundice and contact their physicians at the first hint of symptoms. A potentially fatal liver necrosis is thought to be an allergic hypersensitivity reaction (65).

34.2.8.4.6. Metabolic/Endocrine

Galactorrhea and amenorrhea in women, and excessive weight gain in both sexes have been reported. The galactorrhea and amenorrhea are often successfully managed by dose reduction. The weight gain is not always reversible on TCA discontinuation. Since weight gain can result in potentially serious compliance problems, SSRIs may be reasonable options due to a lesser extent of weight gain associated with their use (65).

34.2.8.4.7. Neurologic/Psychiatric

The delirium secondary to the anticholinergic activity of the TCA is characterized by recent memory loss, disorientation, flushed, dry skin, ataxia, dysarthria, and hallucinations. It is estimated that 8% of patients receiving TCAs experience anticholinergic delirium. With discontinuation, delirium usually clears within 24 to 48 hours. The use of physostigmine is usually reserved for life-threatening overdoses. A fine, resting tremor caused by the TCA is of a faster frequency than the parkinsonian tremor observed with antipsychotics. It does not respond to antiparkinsonian drug therapy but does respond to propranolol. TCAs can lower the seizure threshold. However, this usually occurs only at high therapeutic doses or in overdoses. Thus the presence of a seizure disorder would not contraindicate the use of a TCA. Erectile dysfunction associated with imipramine, desipramine, clomipramine, amitriptyline, and protriptyline (in descending order of potency) are usually the TCAs responsible for causing a disturbance in sexual behavior. The problems are reversible upon decreasing the dose or discontinuing the drug. Drugs with cholinergic action such as bethanechol 20 mg orally 1–2 hours before bedtime appear to correct erectile and ejaculatory impairment (65).

34.2.8.4.8. TCA/MAOI Combination Therapy

A fourteen day period is usually advised between the discontinuation of an MAOI and the initiation of a TCA. An MAOI may usually be started 5 to 10 days after the discontinuation of a TCA, depending on the half-life of the discontinued TCA. The concomitant use of a TCA and an MAOI has been utilized occasionally for the patient unresponsive to a TCA and a MAOI used

separately and sequentially. Reports of hyperpyrexia, seizures, and cardiorespiratory collapse with the combination have been limited to scattered reports when overdoses and other drugs were involved. Although rarely utilized, if this combination is used, it is recommended that all antidepressants be discontinued, 5–10 days for TCA and 14 days for MAOI, before the combination is started, and that preferably amitriptyline 150 mg/day and isocarboxazid be administered simultaneously at conservative doses (65).

34.2.9. Monoamine Oxidase Inhibitors

34.2.9.1. Efficacy

A body of evidence has developed suggesting that there is a diagnostically definable subgroup of depressed patients who are more likely to respond to MAOIs than TCAs. This particular subgroup includes those presenting with atypical depression. A 67% response rate was found with 4 to 6 weeks of phenelzine daily versus a 43% response rate for imipramine, a finding that has been replicated in another study of imipramine-refractory patients with atypical depression (259, 260). MAOIs have also been found more effective than imipramine in treating dysthymia in two controlled trials.

The theory that MAOIs are less effective than TCA in the treatment of major (typical) depression has been widely circulated. However, this perception was based on early efficacy studies that often utilized subtherapeutic or borderline therapeutic MAOI doses. It has also been recognized that the onset of action of MAOI is slower than TCA; therefore, trial design was not optimal for comparisons of the two classes of agents. A meta-analysis of antidepressant efficacy studies calculated antidepressant response rates using intent-to-treat sample (143), found MAOI response rate to be 53% for inpatients and 57% for outpatients, similar to the TCA, SSRI, and TGAD response rates. Therefore, it cannot be generalized that MAOIs are less effective than other agents. Combined results of five studies concluded the MAOIs have been found to be effective in 65% of treatment-refractory depressed patients, comparable to other alternative treatments for refractory depression (65). More recent studies, using larger phenelzine doses (60–75 mg/day), produced more impressive results.

Selegiline, administered as a 24-hour patch, is approved for the treatment of major depressive disorder in adults. Efficacy was established by a 6-week and 8-week randomized controlled trials that established that patch doses of 6 mg, 9 mg or 12 mg per 24 hour patch were more effective than placebo. Additionally, a 25-week continuation treatment trial found the drug more effective than placebo in preventing relapses (261).

34.2.9.2. Dosing

The starting dose of phenelzine is 1 mg/kg/day, usually given on a twice-daily dosage schedule; however, other evidence has suggested that larger doses improve probability of response. There is a wide variability between patients experiencing stimulation or sedation from phenelzine; therefore, the dose schedule should be adjusted appropriately to avoid medication-induced insomnia or sedation. . An adequate therapeutic trial of an MAOI is six weeks. Two weeks are required before the maximum inhibitory effect of phenelzine 30 mg/day is reached, while four weeks are required for a 60 mg/day dose. It is estimated that tranylcypromine 0.7 mg/kg/day is equivalent to phenelzine 1.0 mg/kg/day. When switching a patient from one MAOI to another antidepressant, including tranylcypromine, a 14-day "washout" period is advisable due to the potential risk of a hypertensive crisis and serotonin syndrome (65). When switching from one MAOI to another (besides tranylcypromine), at least a one-week washout interval is advised (262). A summary of the usually recommended antidepressant doses is presented in Table 34.3.

34.2.9.3. Adverse Effects

34.2.9.3.1. Cardiovascular

Phenelzine at a 60 mg/day dose can be expected to significantly decrease the QTc interval of the ECG but not affect the PR interval or the QRS complex. Orthostatic hypotension can also be seen. The blood pressure effects of phenelzine differ from the TCAs in that 1) phenelzine affects both lying systolic blood pressure as well as the orthostatic drops, and 2) the orthostatic hypotensive effects of phenelzine have a slower onset, maximize at four weeks and then appear to decrease in intensity. Patients over 50 years are more likely to experience declines in standing and sitting blood pressure than younger patients are. Initially during the first six weeks of treatment, phenelzine will produce a decrease in systolic and diastolic pressure. However, patients on chronic MAOI therapy for months to years will have their sitting diastolic and systolic pressures increase significantly during the first two hours after ingestion of the dose after which they return to normal (65).

The concomitant ingestion of MAOI and substances containing certain pressor amines has been associated with potentially serious hypertensive crisis. The primary reactions are headache and increased blood pressure resulting from sympathetic overstimulation. Tyramine is the dietary pressor amine usually associated with these reactions. The reactions can also be precipitated by food containing phenylethylamine or dopamine. Normally, MAO found in the gastrointestinal tract inactivates tyramine. However, when MAOIs block this reaction, exogenous tyramine is absorbed and it exerts its indirect pressor action by releasing norepinephrine from the presynaptic storage sites. Therefore, patients taking MAOIs must adhere to strict dietary restrictions. Additionally indirect-acting sympathomimetics such as amphetamines, methylphenidate, ephedrine, pseudoephedrine, phenylpropanolamine, and phenylephrine, have been reported to interact with MAOI.

34.2.9.3.2. Neurologic

These side effects occur rarely but usually include ataxia, tremor, hyperreflexia, paresthesias, and seizures possibly as a result of a pyridoxine deficiency. Pyridoxine 150–300 mg/day for several weeks reverses the paresthesias (263).

34.2.9.3.3. Withdrawal Reactions

The abrupt discontinuation of a MAOI can result in withdrawal symptoms but only rarely. Of the four cases reported, they are characterized by REM rebound producing disturbed sleep and nightmares, hallucinations and delirium. We do not recommend routine tapering of MAOIs because of the infrequency of the withdrawal reactions.

34.2.10. CNS Stimulants

Although substantial anecdotal literature exists suggesting that CNS stimulants may have some utility in depression, the response rates reported in uncontrolled studies have not been replicated in 9 of the 10 placebo controlled trials. However, controlled studies suggest stimulant use may have more validity in the treatment of apathetic "senile" geriatric patients who do not have a primary depression. Partial responses but not remissions are observed in these patients. Although some data suggest that stimulants may be useful in medically ill patients with depression, only one controlled trial of methylphenidate 30 mg/day for three weeks in post-stroke rehabilitation patients suggested improvement in mood and functional independence (264); confirmation of this finding in controlled studies is lacking. The stimulants are reported in uncontrolled studies to be effective in the treatment of TCA-refractory patients. However, controlled studies have reported placebo response rates in this patient population ranging from 57–78% (265).

Fewer ADR are reported with the stimulants than the TCAs. Habituation is commonly described as a risk but it has not been confirmed in control trials. Side effects in decreasing order of frequency include: insomnia, nausea, tremor, appetite change, palpitations, blurred vision, dry mouth, constipation, and dizziness. Signs in their decreasing order of frequency include: blood pressure changes, dysrhythmias, and tremor.

34.3. Mania

Mood stabilizers are utilized for the treatment of patients diagnosed with bipolar affective disorder. Agents available for the treatment of bipolar disorder may be used for the treatment of acute mood symptoms (i.e., depression or mania), or the continuation and maintenance of stabilized symptoms. Agents discussed will include the major mood stabilizing medications utilized. Although antipsychotic agents are commonly used, and some SGA have indications for the treatment of acute mania and/or maintenance treatment of bipolar disorder, those agents were previously discussed.

34.3.1. Lithium

The primary clinical indications for lithium in psychiatry are the treatment of acute manic and hypomanic episodes, maintenance treatment of patients with recurrent bipolar-I and -II and unipolar affective disorders, and as an augmenting agent for acute refractory major depressive disorder. The American Psychiatric Association Practice Guidelines for the Treatment of Patients with Bipolar Disorder Working Group has recommended lithium or valproate plus an antipsychotic as the first-line treatment for severe mania. For a less severe manic episode, treatment with lithium, valproate, or an antipsychotic as monotherapy may be sufficient (266).

34.3.1.1. Efficacy

34.3.1.1.1. Mania

In the initial treatment of an acute manic episode, a three-week trial of lithium is recommended. The onset of action of lithium is often delayed one to two weeks (267). Substantial improvements in symptoms are often noted by the third week. Once the patient starts to improve, symptom resolution often occurs quickly. Abrupt discontinuation in the manic phase may result in rapid relapse, possibly within several days. Lithium monotherapy may be warranted for a manic patient not acutely agitated. In the placebo-controlled studies conducted to investigate lithium's efficacy in the treatment of acute mania, 70% of all lithium treated patients experienced at least partial reductions in manic symptoms (268–271). Elderly patients with mania treated with lithium also appear to respond similarly, although some patients may not tolerate typical antimanic lithium levels (272).

Lithium has been compared to the FGA chlorpromazine, haloperidol and pimozide in nine controlled trials (80, 81). The results of these studies, in general, showed that 1) the percentage of patients showing remission or marked improvement after three weeks of treatment was greater with lithium than with a FGA; 2) lithium is particularly effective in ameliorating the affective and ideational symptoms associated with mania, whereas the antipsychotic is initially superior to lithium in controlling psychomotor activity; 3) inpatients treated with lithium are more likely to be discharged at the end of a three-week treatment period compared to patients receiving a typical antipsychotic alone (273). In appropriate doses ($\geq$1800 mg/day or $\geq$0.8 mEq/L), lithium produces marked improvement or remission in $\geq$70% of patients. The probability of patients showing remission or marked improvement of manic symptoms is greater with lithium than with FGA. Lithium is particularly effective in ameliorating the affective and ideational symptoms associated with mania, whereas, FGA are superior to lithium in controlling, at least initially, the increased psychomotor activity associated with mania. Hospitalized patients with mania were discharged sooner if they were treated with lithium as opposed to a FGA.

Three controlled trials have assessed the comparative effectiveness of lithium and SGA for treating acute mania. Olanzapine (10 mg/day), quetiapine (up to 800 mg/day), and risperidone (6 mg/day) (274–276), were studied, with similar improvements noted between all medications. However, the lithium doses in these studies (800 to 1,000 mg/day) resulted in subtherapeutic lithium concentrations for many patients in the lithium group thereby biasing the studies in favor of the SGA.

The rationale for lithium-antipsychotic combinations in the treatment of acute manic episodes is that the antipsychotic will rapidly control hyperactivity and irritability, whereas lithium may take longer to exert effect on the core manic symptoms. The antipsychotic, if used, is started immediately for controlling hyperactivity. When the patient's symptoms are controlled and behavior normalizes, the antipsychotic is discontinued. The sole study that has evaluated this strategy with FGA concluded that the lithium-haloperidol combination produced slightly greater symptom control than haloperidol alone (81). The SGA risperidone (3.8 mg/day) has been compared to haloperidol (6.2 mg/day) and placebo in the augmentation of mood stabilizer therapy. Both antipsychotics combined with mood stabilizer were more effective than mood stabilizer monotherapy (278). Quetiapine has been evaluated in two studies; the first concluded that quetiapine (584 mg/day) combined with mood stabilizers lithium or valproate was more effective than mood stabilizers alone, and the second concluded that quetiapine (492 mg/day) combined with mood stabilizer was more effective than the antipsychotic monotherapy (277, 278).

Lithium in combination with lorazepam was found to be as effective as lithium combined with haloperidol in response and time of onset in a controlled trial (279). However, more patients dropped out in the lorazepam combination group due to nonresponse, while more patients dropped out of the haloperidol group due to ADR. After manic symptoms resolve, an attempt should be made to taper the benzodiazepine (usually over a week) then discontinue.

34.3.1.1.2. Major Depressive Disorder

Sixty to eighty percent of patients in the depressive phase of bipolar disorder responded to lithium monotherapy in a review of 13 studies (267). If a patient has been compliant with lithium, adding lamotrigine or a standard antidepressant should be considered. Lithium's antidepressant effects are usually apparent within three weeks, but may take as long as six weeks. A therapeutic trial is considered 4–6 weeks in length (280). Lithium is sometimes used as an augmentation strategy for treatment-refractory depression. Lithium is not usually used as monotherapy for unipolar depression as only 30–40% of patients may respond. Patients with mixed episodes or rapid cycling ($\geq$4 episodes per year) forms of mania or concurrent substance abuse have been reported to be less likely to respond to lithium than to valproate or carbamazepine. This conclusion, however, was not derived from controlled studies. A meta-analysis of 16 maintenance studies suggested that there was no evidence that mood stabilizers lithium, valproate, and carbamazepine differed in efficacy for treating rapid cycling (281). Patients responding to lithium are more likely to have a bipolar diagnosis with a positive family history of bipolar or unipolar illness. Patients with unipolar depression who responded to lithium were likely to have endogenous depression and a positive family history of depression (282). Good responders were less likely to have personality disorders.

34.3.1.1.3. Continuation and Maintenance Treatment

Continuation treatment consists of uninterrupted pharmacologic management for 4–6 months after the acute episode is resolved, and is used to prevent relapse (exacerbation of current episode). Maintenance treatment is geared towards preventing a recurrence (a new episode). If the patient is not a candidate for maintenance treatment, lithium may be discontinued at the end of the continuation phase. Tapering lithium for a two to four week period significantly reduces the chance for relapse (283), which is especially important since abrupt discontinuation may lead to a rapid return of manic symptoms in some patients (284). Conservative recommendations for discontinuation would be a four-week taper period, accomplished by decreasing lithium dose by 25% weekly. A conservative recommendation for antimanic therapeutic lithium concentrations would be to maintain concentrations (0.9–1.4 mEq/L) for 3–6 months after symptom resolution (285). If lithium is used to treat depressive episodes, it should be continued at antimanic plasma levels for 4–6 months after response (286).

Lithium is extremely effective in preventing recurrences of bipolar-I and -II episodes, according to a meta-analysis (287). The recurrence rate of bipolarity on lithium was 32%, compared to 82% for placebo-treated patients. Most patients with bipolar disorder experience multiple episodes. Among bipolar patients, it is recommended that maintenance treatment should be initiated after two episodes, especially if the second episode occurred within five years of previous episode (286). After first-episode mania, it is generally recommended to continue lithium for additional 3–6 months (following acute response) and then discontinue the drug. However, there may be situations where maintenance treatment may be desired following the first episode. Some potential considerations are complications resulting from the first episode (legal, economic, sexual indiscretions, suicide attempt) and the high risk of relapse. Lithium monotherapy in maintenance is recommended although some patients respond better to a combination of lithium and a tricyclic antidepressant (267). Antidepressants imipramine and paroxetine were more effective than placebo in patients already taking lithium when lithium concentrations were greater than 0.8 mEq/L, although no difference in recurrence was found between the antidepressants and placebo when all lithium-treated patients, regardless of blood level, were included in the analysis (161). There has been concern regarding the possibility of antidepressant use among bipolar depressed patients causing manic or hypomanic symptoms. The most recent findings were a 25% switch rate within one year (288).

The estimated suicide rate for patients hospitalized with unipolar and bipolar affective disorder ranges from 8–20% (289). A substantial body of data now suggests that lithium maintenance therapy decreases the risk of suicide in this patient population (290).

34.3.1.2. Dosing

34.3.1.2.1. Acute Mania

The generally recommended therapeutic range for lithium is 0.9–1.4 mEq/L. Patients with levels > 1.4 mEq/L experience no greater improvement in their manic symptoms than patients with lower serum lithium concentrations. Patients with concentrations less than 0.9 mEq/L usually do not experience a complete remission of their manic symptoms. Figure 34.1 presents a dosing nomogram useful for the initial dosing of acutely manic patients. Control of symptoms usually occurs within 4–10 days after the beginning of treatment depending upon how quickly the lithium dose reaches the therapeutic range. Acutely manic patients tolerate and require higher lithium doses due to their increased lithium clearances. The initial doses are not tolerated once the manic episode begins to abate since lithium clearance decreases and the lithium levels increase as the symptoms resolve because of the patient requiring more sleep. Thus, lithium levels ought to be drawn twice weekly when treating an acutely manic patient because of the predictable but potentially toxic paroxysmal increase in the lithium level as the manic hyperactivity begins to resolve. A summary of the usually recommended mood stabilizer doses is presented in Table 34.4.

34.3.1.2.2. Major Depression

The target lithium level for acute treatment of major depressive disorder is 0.9–1.4 mEq/L (267).

34.3.1.2.3. Continuation Treatment

The recommended lithium concentration for continuation treatment is 0.9–1.4 mEq/L (267).

34.3.1.2.4. Maintenance Treatment

The ideal prophylactic or maintenance therapy serum lithium concentration is debatable based on findings of considerable variance between several English and one American study. Overall, these data have led us to conclude that serum lithium concentra-

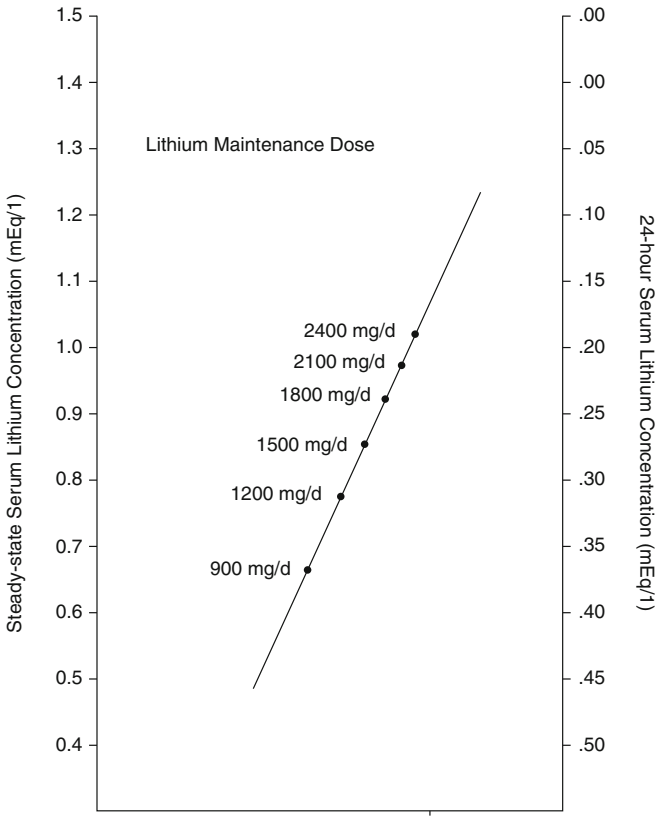

FIGURE 34.1 Lithium dosing nomogram for predicting steady-state serum concentrations for 900–2400 mg/day maintenance doses following a 1200 mg lithium carbonate test dose and then measuring the 24-hour serum lithium concentration. Reprinted from (403) Annals of Pharmacotherapy, copyright (1987) with permission from SAGE Publications, Inc.

TABLE 34.4 Adult dosages for US available mood stabilizers.

Generic name	Trade name	Initial dose (mg/day)	Usual dose range (mg/day)
Carbamazepine	Tegretol	400	400–1600
Lithium	Eskalith	Acute mania 600–1800** 0.6–1.2 mEq/L**	Maintenance 900–1200** 0.45–0.6 mEq/L
Lamotrigine	Lamictal	25 (no inducer drugs)* 25 (added to valproate)* 50 (added to other inducers)	200 (no inducer drugs)* 100 (added to valproate)* 400 (added to other inducers)
Oxcarbazepine	Trileptal	600	600–2400
Valproic acid	Depakote Depakene	750**	750–4200**

*Inducer drugs include drugs such as barbiturates, carbamazepine, phenytoin and St John's Wort.
**Dose changes made by the editor.

tions between 0.45 to 0.59 mEq/L on a single daily dose schedule is appropriate in the prophylactic treatment of affectively ill patients although higher concentrations are required in the elderly. However, patients should increase their dose by 1.5 times at the first signs of any manic or depressive symptoms and then slowly taper downward to the lower concentration as the symptoms resolve (65).

34.3.1.2.5. Serum Lithium Concentration Sampling

Lithium levels are usually obtained 12 hours after the last dose. The half-life of lithium in psychiatric patients has been estimated to range from 15 to 55 hours. Patients over the age of 65 should have levels drawn every 6 months while younger patient every 6–12 months assuming clearance is not perturbed by episodes of diarrhea, vomiting, or dehydration. Adding or discontinuing an interacting medication, or a change in renal function, would indicate the need to draw a lithium level 5 to 10 days later. Manic patients who have been discharged from the hospital after acute treatment should continue to be monitored as

outpatients, with lithium levels obtained every two weeks for several months in order to detect any changes in clearance. There is no universally accepted consensus recommendation for lithium level monitoring in the stable outpatient population. After about four months it is recommended to switch the patient to single daily dosing. Patients generally can tolerate up to 1500 mg/day as a single dose. Single daily dosing is preferred in patients because it results in less polyuria than divided daily dosing. If the clinician assumes a 24-hour half-life for the patient, then an approximate 20% increase in the 12-hour steady-state serum lithium concentration ought to be anticipated when switching from divided to single daily dosing. However, an even more reasonable and conservative estimate of the increase in the steady state level would be to expect a 0.2 mEq/L increase (65).

34.3.1.2.6. Product Formulations

Lithium formulations in the United States include lithium immediate-release capsules and tablets, sustained release products, and lithium citrate syrup. Slow-absorption lithium product formulations were developed in an attempt to decrease the ADR associated with peak and rapidly rising serum lithium concentrations as well as to increase compliance; the only comparison study of regular-release lithium to the slow-release lithium product available in the U.S. did not demonstrate a difference in the ADR profile of the two formulations (291). One bioavailability study reported that the areas-under-the-curve and the 12-hour lithium concentration of an immediate-release lithium tablet and the two sustained-release products did not significantly differ (292). Therefore, patients may be switched between an immediate-release lithium product and a sustained-release product on an mg for mg basis. Sustained-release lithium products should be swallowed completely, without crushing or chewing. The citrate syrup is useful in patients who experience watery diarrhea from the osmotic cathartic effect of lithium on the colon. Because the lithium is already in solution, more absorption occurs in the upper end of the gastrointestinal tract making it less likely for unabsorbed lithium to reach the colon.

34.3.1.2.7. Retrospective Dosing—Steady-State Concentration Monitoring

As lithium dose increases or decreases, the steady-state serum lithium concentration increases or decreases respectively in direct proportion to the change. A patient with a steady-state concentration of 1.0 mEq/L at 1200 mg/day will have a steady-state concentration of 1.50 mEq/L if the dose is increased to 1800 mg/day, whereas if the dose is decreased to 600 mg/day, the steady-state concentration should be 0.50 mEq/L.

34.3.1.3. Adverse Effects

During the first week of lithium treatment there are numerous ADR reported by the newly initiated patient, including primarily gastrointestinal irritation, tremor, muscle weakness, and polydipsia/polyuria. Lithium mainly affects the nervous, renal, gastrointestinal, and metabolic systems. The frequency of ADR involving these systems ranges from 20–40%, dependent upon the patient's lithium level. Less common ADR include the skin, heart, and thyroid gland. Direct questioning concerning ADR in patients receiving lithium prophylactically found the following incidences: polyuria and polydipsia, 79%; tremor, 45%; loose stools, 20%; weight gain greater than 10 kg, 20%; edema, 10%; dermatitis, 3%; and muscle weakness, 1.6% (293). It is estimated that 60–90% of patients maintained on lithium at a level of 1.0 mEq/L will report at least one ADR. Lithium levels of 0.4–0.6 mEq/L will significantly reduce the amount of patients who experience ADR (267, 285).

34.3.1.3.1. Central Nervous System

Delirium manifested by distractibility, poor memory, disorientation, incoherence, poor concentration, and impaired judgment occurs predictably at supratherapeutic and rarely at therapeutic lithium levels. The organic symptoms may be accompanied by involuntary movements, ataxia, and dysarthria. The symptoms often appear insidiously and maybe unrecognized as lithium related. CNS compromised patients (e.g., seizure disorders, schizophrenia) may be predisposed to this ADR, so in this latter patient population lithium should be dosed conservatively. Usually, however, the symptoms of lithium intoxication do not begin to exhibit themselves until the serum concentration exceeds 1.5 mEq/L. As mentioned above, clinical manifestations are primarily neurologic, (i.e., confusion, poor concentration, clouding of consciousness, delirium, and coma). Cerebellar disturbances are manifested by dysarthria, nystagmus, and ataxia (294).

34.3.1.3.2. Dermatologic

Lithium has been associated with a wide range of dermatologic problems of varying clinical significance. Transient maculopapular eruptions and follicular eruptions, which often remit spontaneously, are usually not significant problems. However, exacerbations of acne and psoriasis may be severe enough that compliance may become a problem (295).

34.3.1.3.3. Gastrointestinal

GI complaints include epigastric bloating, slight abdominal pain, nausea, vomiting, and anorexia. Fortunately, these ADR are transient. They are minimized by administering the lithium with food and by dividing the total daily dose into small divided doses and possibly by utilizing a slow-release dosage form of lithium. Loose stools, diarrhea, and occasional bloody stools are a far more serious problem because the sodium and water loss predisposes the patient to lithium retention and a potential intoxication. The diarrhea results from the unabsorbed lithium in the colon acting as an osmotic cathartic. The problem can be circumvented by utilizing the more quickly liquid lithium citrate product formulation (65).

34.3.1.3.4. Hematologic

Both leukocytosis and thrombocytosis occur in the majority of patients receiving lithium. However, both are regarded as innocuous ADR. The leukocytosis is not marked by a 'left shift'. The peak elevation typically occurs within one week and is reversible within 1 to 2 weeks. The elevated platelet counts may require 2 to 4 months to normalize (65).

34.3.1.3.5. Endocrine

Weight gain of > 10 lb are estimated to occur in 11–64% of patients taking lithium. Studies report weight gain ranging 3 to 28 kg, with an average of 8.5 kg over 6 months to 17 years. It is important to inform patients of the potential for weight gain and to avoid high calorie soft drinks in replacement of fluid loss secondary to polyuria. Thyroid hypofunction is the most common thyroid abnormality associated with lithium with an estimated prevalence of 0–23%. Patients developing hypothyroidism are most commonly women over 40 years of age. Treatment may not be necessary as the majority of cases of lithium-induced thyroid abnormalities are transient and often present without clinical symptoms. Despite the lack of a dose-response relationship, some clinicians report lowering the dose may reverse the hypothyroid symptoms. Goiter and the hypothyroid state can be reversed with thyroid supplementation. Pre-existing hypothyroidism is not an absolute contraindication to lithium treatment. Lithium can increase serum calcium, reduce serum phosphorous, and increase parathyroid hormone (PTH) in about 10–15% of patients. Complications of primary hyperparathyroidism do not occur, though osteopenia has been reported. Hypercalcemic patients taking lithium can appear dysphoric, apathetic, or ataxic. Thus patients appearing psychomotor retarded or depressed ought to have their calcium monitored before antidepressant therapy is started (65).

34.3.1.3.6. Neuromuscular

Lithium-induced tremor is reported to occur in 4–65% of patients (296). It may occur at rest and during purposeful movements. Worsening of the tremor or extension to other parts of the body can be regarded as a prodromal symptom of impending lithium toxicity. Additionally, emotional stress and excessive caffeine intake may also worsen the tremor. However, because of its diuretic effect reducing caffeine intake may increase lithium levels and worsen tremor. Decreasing the dose is an effective means of management. If this is not effective, the beta-blocker, propranolol 30–80 mg/day is an alternative. Muscle weakness, a transient side effect, appears to be dose-related and disappears with reduction or discontinuation of lithium (65).

34.3.1.3.7. Renal

Although lithium-induced polyuria and polydipsia are common, they are usually reasonably well-tolerated by the patients and completely or partially reversible upon the discontinuation of the lithium therapy. Severe cases can result in serious fluid and electrolyte disturbances that could result in toxicity. Since polyuria is a predisposing factor toward potential future renal dysfunction, it is imperative to minimize the degree of this ADR. Maintaining a lithium level between 0.4–0.8 mEq/L will minimize this ADR. The use of single daily dosing may help to prevent polyuria. The diuretics hydrochlorothiazide 50 mg/day, or amiloride 10–20 mg/day have been used. Thiazides may reduce lithium clearance and produce hypokalemia, while amiloride may produce elevations in potassium levels. Additionally, renal function in these patients should be monitored closely. The most practical method available to routinely monitor renal function is the use of the Cockcroft-Gault method (297) for estimating creatinine clearance (Cl Cr), where

$$\mathrm{ClCr} = (140\text{-age})(\text{kg body-weight})/(72)(\text{fasting serum creatinine})$$

There are three important points to remember about the use of the above equation to insure its accuracy: 1) the calculated Cl Cr should be reduced by 15% in women, 2) a correction to lean or ideal body weight is necessary in excessively obese, edema-

tous patients; and 3) the serum creatinine value should be drawn in the fasting state. Lean body weight can be calculated from the following two formulas (298):

- Ideal Body Weight (in kilograms)$_{men}$ = 52 kg + 1.9 kg for each inch over 5 feet
- Ideal Body Weight (in kilograms) $_{women}$ = 49 kg + 1.7 kg for each inch over 5 feet

The Cl_{Cr} ought to be estimated by this method ideally every 6–12 months (65). Morphological changes in the kidneys have been associated with lithium treatment. Unique distal nephron lesions have been associated with long-term lithium treatment (299). These changes, which may be associated with polyuria, may or may not be reversible.

34.3.1.3.8. Overdose

Mild intoxications present with symptoms that include lethargy, drowsiness, fine tremor, anorexia, nausea, vomiting, and diarrhea. As the blood level increases, increasing CNS involvement occurs. These symptoms may include marked impairment of consciousness, hyperreflexia, coarse generalized tremors, restlessness, muscle fasciculation, myoclonic and choreoathetoid movements, dysarthria, seizures, ataxia, and coma (300). Symptoms of toxicity generally occur at lithium level greater than 2 mEq/L.

34.3.1.3.9. Teratogenicity and Lactation

Lithium is listed as a pregnancy risk factor D medication. Lithium has been associated with cardiovascular malformations such as Ebstein's anomaly and others. More recent epidemiologic and case control studies have reported a risk of 0.023% in control patients and 0.056% in lithium-treated patients, which is not statistically significant (301). Recommendations for the use of lithium during pregnancy are as follows (301).

- Appropriate contraceptive practices should be used to minimize unplanned drug exposure.
- Women who have experienced a single affective episode should gradually taper and discontinue lithium before becoming pregnant and should remain lithium-free throughout pregnancy.
- Women at substantial risk of relapse should discontinue lithium during the first-trimester of pregnancy and should consider re-introduction only if clinical deterioration occurs.
- Women at an unacceptable risk of relapse should maintain lithium use throughout pregnancy.
- Women exposed to lithium during the first-trimester should receive reproductive counseling as well as fetal echocardiology and high-resolution ultrasound examinations at gestational weeks 16 through 18 weeks' (301).

Lithium is excreted in the breast milk at a concentration about 40–50% that of the mother's serum. Infants may be at increased risk for lithium toxicity. Therefore, the American Academy of Pediatrics considers lithium to be contraindicated during breast-feeding (302).

34.3.2. Valproic Acid

34.3.2.1. Efficacy

Valproic acid received FDA indication for the treatment of acute mania in 1995. The extended release dosage form is also approved for the acute treatment of mixed episodes associated with bipolar disorder. Although not FDA-approved, the augmentation of lithium with valproate for maintenance therapy of bipolar-I disorder may lead to decreased risk of relapse and recurrence (303).

34.3.2.1.1. Acute Manic and Mixed episodes

Controlled trials demonstrated the efficacy of valproate in comparison with other treatments for acute mania (304). Valproate was shown to be equivalent to lithium and carbamazepine, and less effective than olanzapine. Olanzapine was only more effective than valproate for reducing psychomotor activity, sleep, and flight of ideas (305). Olanzapine was associated with more weight gain and sedation than valproate, but there were no differences in acceptability as measured by withdrawals. One large, multi-center study comparing lithium with valproate reported that > 50% of both patient groups exhibited a greater than 50% reduction in symptoms of mania (271). However, > 50% of the patients in the lithium group had previously failed lithium, and the patients responding to lithium in the study improved more than the patients responding to valproic acid. A meta-analysis of maintenance studies suggested that there was no evidence to suggest that valproate, lithium, and

carbamazepine differ in efficacy for the treatment of rapid cycling (281). There is no evidence that valproate dose can be tapered and still reduce rate of manic or depressive episodes in continuation treatment. If valproate were to be discontinued, decreasing the dose by 25% at weekly intervals would be a conservative taper schedule. A 52-week maintenance trial of valproate, lithium, and placebo showed no difference for any group in time to recurrence of mood episode. This study is considered a failed study since it is accepted fact that lithium is more effective than placebo as a maintenance treatment for bipolar affective disorder. Thus any study that uses both lithium and placebo comparators and cannot show a difference has to be assumed to have serious design or data analysis flaws. There are no published controlled trials of valproate treatment of major depressive disorder, but one unpublished report did not differ from placebo in partial response rates (266).

34.3.2.2. Dosing

The use of the enteric-coated formulation of valproic acid, divalproex sodium, is essential to minimize gastrointestinal complaints. All valproic acid formulations are rapidly absorbed after oral ingestion with the exception of the enteric-coated divalproex sodium, whose absorption is delayed by about 2–4 hours. Most patients can be treated with 1,000 to 1,500 mg total daily dose. The required dosage may range from 750 mg to 6,000 mg daily. The manufacturer recommends starting at a dose of 25 mg/kg/day (if using the extended release formulation, given in one dose). Once the daily dose is stabilized, divalproex may be given once or twice daily. The extended release formulation may be given once daily. Once daily doses given at bedtime reduce ADR (306). Blood levels are drawn 12 hours after the last dose. A therapeutic concentration range of 85–125 mcg/ml results in a higher probability of response than lower levels (307). This recommendation needs to be replicated in a fixed dose study. A response should be anticipated usually within a few days of attaining a therapeutic blood level, although a therapeutic trial is a minimum of three weeks (65). Valproate levels may be obtained 3 days after a patient reaches a steady dose, but can be taken earlier if the patient experiences adverse effects. Clinical response is an important indicator of medication dose as well. There are no evidence-based recommendations for the frequency of valproate monitoring in stable outpatients. The addition or discontinuation of an interacting medication, or change in liver function, would indicate a valproate level within 2 to 4 days (11). A summary of the usually recommended mood stabilizer doses is presented in Table 34.4.

34.3.2.2.1. Dosage Forms

Divalproex is available in two oral forms: a delayed release enteric coated divalproex, and an extended release formulation of the enteric-coated divalproex. Bioavailability for the extended release formulation is 8–20% less than the regular enteric-coated product; therefore, the manufacturer has published recommendations for switching patients from one product to the other. Additional formulations available include a syrup, soft gelatin capsule, and coated pellets encapsulated to be sprinkled on food (306, 308). The enteric coated tablets and sprinkle products are divalproex sodium, which is a 50%/50% combination of sodium valproate and valproate. These two products reduce the gastrointestinal ADR of valproate by reducing mucosal contact, slowing the rate of absorption, and lowering the peak valproate concentration (see gastrointestinal ADR below). The extended release enteric-coated tablet's absorption may be so delayed that distribution may still be occurring at 12 hours after a dose (309). A true trough may not occur until 14 to 16 hours after the last dose. Therefore, if the extended release dosage form is utilized, it is recommended that blood levels be drawn 18 hours after the last dose. When switching from delayed-release to extended-release formulation, the daily dose needs to be increased by an average of 12% to achieve comparable plasma concentrations (310).

34.3.2.3. Adverse Effects

34.3.2.3.1. Cardiovascular

Edema, tachycardia, hypertension, palpitations, and hypotension have all been associated with the use of valproic acid (303).

34.3.2.3.2. Central Nervous System

The most common CNS effect of valproic acid is sedation that is observed in 4% of patients (65). Less commonly, patients may experience confusion, dizziness, and headache. Hyperammonemic encephalopathy has been reported in patients with urea cycle disorders (311).

34.3.2.3.3. Dermatologic

Transient alopecia has been reported in three studies in 4% of patients treated with valproic acid. Skin reactions are uncommon.

34.3.2.3.4. Endocrine

Weight gain and increased appetite are commonly observed in patients receiving valproic acid. Idiosyncratic pancreatitis is a potentially fatal but rare adverse reaction associated with valproic acid. Symptoms may include abdominal pain, nausea, vomiting, and anorexia. Abdominal pain associated with increased amylase level demands that the drug be discontinued immediately (65).

34.3.2.3.5. Gastrointestinal

These are the most commonly reported ADR associated with valproic acid. They present as anorexia (11.6%), indigestion, heartburn, nausea (13.8%), vomiting (19.2%), and/or transient diarrhea (1.7%). It is approximated that 85% of the patients unable to tolerate the standard formulation can be successfully switched to the enteric-coated form of the drug.

34.3.2.3.6. Hepatic

Increases in hepatic transaminases have been reported in 2–44% (306). With discontinuation, dose reduction, or continuation, the enzymes will return to baseline values. Baseline liver function tests are recommended prior to initiation. One group of authors recommended affective disorder patients should have these tests monthly for the first several months and then every 6 to 24 months thereafter. Potentially fatal idiosyncratic but rare (1 per 37,000) hepatotoxicity is associated with valproic acid. Risk factors include age younger than 2 years, mental retardation, inborn errors of metabolism, use of multiple anticonvulsants, and difficult to control seizures (309). However, fatalities have only occurred in children less than 10 years old (65).

34.3.2.3.7. Teratogenicity and Lactation

Valproate is listed as a pregnancy risk factor D medication. There is an increased risk (1–2%) of neural tube defects in children exposed to valproic acid with or without other antiepileptic drugs in the first trimester of pregnancy (312). Valproate exposure has also been associated with minor facial defects (313). Women who have been exposed to valproate during 17th through 30th days of gestation should consult their clinician about prenatal testing (313). No adverse reactions from valproate exposure in the nursing infant have been reported (313). The medication is compatible with breastfeeding (314). Since valproic acid is excreted in the breast milk, breast-feeding is not recommended.

34.3.3. Carbamazepine

The extended release form of carbamazepine is FDA-indicated for the treatment of acute manic and mixed episodes in patients with bipolar-I disorder (303). Although not indicated for the following, carbamazepine has shown efficacy for maintenance treatment of bipolar disorder, bipolar patients nonresponsive to lithium, and in combination with lithium after the failure of both agents (303).

34.3.3.1. Efficacy

34.3.3.1.1. Acute Mania

The onset of action of carbamazepine in acute mania varies from 1 to 2 weeks (315), and a therapeutic trial is considered three weeks in length. Carbamazepine has comparable efficacy with lithium and chlorpromazine (316–319). Compared to valproate, it was less effective, and more "rescue medications" were needed (320). Overall, most experts suggest that carbamazepine is probably as effective as lithium and valproate in treating acute manic episodes (321).

34.3.3.1.2. Major Depressive Disorder

Carbamazepine is not effective in the treatment of depression (322).

34.3.3.1.3. Maintenance Treatment

Controlled trial data have shown the effectiveness of carbamazepine as a maintenance treatment for recurrent bipolar disorder to be spotty. In a study with an observation period of 2.5 years, classical non-delusional bipolar patients had a lower rehospitalization rate with lithium than with carbamazepine prophylaxis whereas there was no difference in effectiveness among the non-classical bipolar patients, i.e., mixed and rapid cyclers (323). Hospitalizations and affective disorder recurrences did not differ between the drugs, but among study completers the recurrences occurred in 28% of the lithium treated patients versus 47% of the carbamazepine treated patients. Patients on lithium required less psychotropic co-medication and experienced fewer severe ADR (284). The largest maintenance treatment study suggests a therapeutic advantage favoring lithium versus carbamazepine but the combination of the two is the most effective treatment (324).

34.3.3.2. Dosing

The initial dose is 200 mg given twice daily with meals and increased in 200-mg increments every other day. Initial target doses are recommended to be 10 to 15 mg/kg/day. After two weeks at this dose, the dose may be increased due to hepatic autoinduction of metabolism (325, 326). Most patients will require doses ranging from 600 to 1,600 mg/day; some patients may require up to 2,000 to 3,000 mg/day. Serum levels should be obtained in the morning 12 hours after the last dose (327). A serum level might be obtained after the target dose is achieved and the patient has been on carbamazepine for at least two weeks. Since carbamazepine stimulates its own hepatic metabolism, steady-state plasma concentrations may be 50% below the expected values. Maximal hepatic enzyme induction reportedly occurs within 3–5 weeks; therefore, serum sample drawn after this time should reflect a true steady-state concentration. Any further changes in the carbamazepine dosage will require approximately one week for concentrations to reflect the new steady-state concentration (325). In a nonresponding patient, a linear dose increase to obtain a level of 10 to 12 mcg/ml might be tried. A repeat carbamazepine level might be obtained three days after the target dose is reached. There are no guidelines for the frequency of obtaining carbamazepine levels in a patient stabilized on carbamazepine. A level might be obtained if there is a change in the patient's clinical condition such as a manic relapse to check for compliance, an acute delirium to check for a toxic level > 12 mcg/ml or if a drug interaction is suspected in cases of either relapse or toxicity. There is no evidence that maintenance doses differ from antimanic doses (11). Likewise, there is no accepted therapeutic range for maintenance treatment of affective disorders. There is no evidence suggesting that maintenance doses differ from antimanic doses (11). A summary of the usually recommended mood stabilizer doses is presented in Table 34.4.

34.3.3.2.1. Dosage Forms

Carbamazepine is available as an immediate release tablet, a chewable tablet, a suspension, and as two extended release formulations.

34.3.3.3. Adverse Effects

The chemical structure of carbamazepine resembles a TCA. Thus, most of its ADR profile resembles that of a TCA.

34.3.3.3.1. Cardiac

Carbamazepine can suppress both atrioventricular conduction and ventricular automaticity. However, significant ECG changes have only been reported in patients with pre-existing conduction disturbances. The drug is contraindicated in patients with bundle branch blocks (65). Other reported cardiovascular events include congestive heart failure, aggravation of hypertension, hypotension, syncope and collapse, edema, vasculitis, aggravation of coronary artery disease, primary thrombophlebitis, and recurrence of thrombophlebitis. Some of these cardiovascular effects have resulted in death (328).

34.3.3.3.2. Central Nervous System

CNS ADR of dizziness (29%), ataxia (21%), clumsiness (17%), and drowsiness (13%) usually occur at the start of therapy (329). Delirium and hallucinations are a result of central anticholinergic activity. Dystonic reactions, dopamine blockade can occur two to three weeks after the start of therapy (65).

34.3.3.3.3. Dermatologic

Carbamazepine-induced dermatologic reactions occur in 2–12% of patients (330, 331). The reactions occur within the first 5 months of treatment. They include rashes with or without edema, systemic lupus erythematosis, dermatomyositis, erythema

multiforme, and Stevens-Johnson syndrome. Resolution of the rashes occurs on discontinuation of the drug although concomitant antihistamines allow some patients to continue treatment. Patients presenting with Stevens-Johnson syndrome should discontinue carbamazepine and should not be rechallenged (65).

34.3.3.3.4. Endocrine/Metabolic

Carbamazepine is a vasopressin agonist and can cause hyponatremia and water intoxication. When administered with lithium, the hyponatremia has precipitated lithium intoxication reaction (65). Carbamazepine may increase hepatic clearance of thyroid hormones and have an inhibitory effect at the hypothalamic level (328, 332).

34.3.3.3.5. Gastrointestinal

Nausea (8%) is the most frequent ADR that occurs during the initiation of carbamazepine therapy (329). Less frequently, diarrhea and abdominal cramps have been reported.

34.3.3.3.6. Hematologic

A transient mild leukopenia occurs in approximately 10% of patients following the start of therapy but it normally resolves within the first four months of treatment. Although relatively rarely reported, aplastic anemia (27 cases) and agranulocytosis (23 cases) are associated with carbamazepine. The following conservative approach to the monitoring of possible bone marrow function is suggested: 1) if baseline complete blood count (CBC) is in the middle to upper range no further monitoring is recommended; 2) if baseline CBC is in the low-normal or below-normal range the CBC should be measured every 2 weeks for the next 1–3 months; and 3) if the white count falls below 3000/mm^3 the dose should be decreased or the drug discontinued. Because of the rapid onset of aplastic anemia, agranulocytosis, and thrombocytopenia, the patient must be educated to immediately contact his/her physician at the first sign of an infection, fever, fatigue, ecchymosis and/or mucous membrane bleeding (333).

34.3.3.3.7. Hepatic

Up to 20% of patients receiving carbamazepine may have elevated liver enzymes (334). Most levels stabilize and do not continue to rise. In rare cases, cholangitis, cholestatic and hepatocellular jaundice, hepatorenal failure, abnormal liver function tests and hepatic failure (very rare cases) have been reported (309).

34.3.3.3.8. Ophthalmologic

Visual disturbances such as blurred vision, transient diplopia, and oculomotor disturbances, lens opacities, and conjunctivitis have been reported, usually not occurring at doses less than 1,200 mg daily (330).

34.3.3.3.9. Teratogenicity and Lactation

Carbamazepine is a categorized as a pregnancy risk factor D drug. A study utilizing retrospective and prospective data has demonstrated that carbamazepine is a teratogenic agent The anomaly incidence was 11% for craniofacial defects, 26% for fingernail hypoplasia, 1% for spina bifida, and 20% for developmental delay (335, 336). However, other reports have suggested no adverse fetal effects. Birth defects reported in 123 pregnancies associated with the use of carbamazepine included nervous system defects, urinary tract malformations, heart deformations, and craniofacial or skeletal abnormalities (337). Carbamazepine was reported not to adversely affect the global IQ of children born to mothers treated with carbamazepine alone (336). Carbamazepine in breast milk produced nontoxic plasma concentrations that averaged 0.4 mcg/ml (338). The milk to plasma ratio of carbamazepine ranges from 0.24–0.69 (313). The drug is compatible with breast-feeding (314).

34.3.4. Lamotrigine

34.3.4.1. Indications

Lamotrigine is FDA-approved in the maintenance treatment of bipolar-I disorder to delay the time to occurrence of depressive episodes in patients treated for acute mood episodes with standard therapy (303).

34.3.4.2. Efficacy

Acute Treatment: Three published and four unpublished controlled trials have evaluated the use of lamotrigine in the acute treatment of affective mood disorders (339–342). The majority of the data suggests that lamotrigine is no more effective than placebo in the short-term treatment of mania or depression.

34.3.4.2.1. Maintenance Treatment, Bipolar I Affective Disorder

Controlled trials established the efficacy of lamotrigine as an effective prophylactic agent to prevent recurrences of mood episodes. Compared to placebo lamotrigine up to 400 mg/day roughly doubled the time between affective episodes (343, 344).

34.3.4.2.2. Maintenance Treatment, Bipolar I or II Affective Disorder with Rapid Cycling

Studies that assessed the effectiveness of lamotrigine among patients diagnosed with bipolar rapid cycling illness concluded that lamotrigine was no more effective than placebo (339, 345). Lamotrigine was no better than placebo in reducing the time between episodes in one published and one unpublished study (339, 345).

34.3.4.3. Dosing

Patients not taking an enzyme inducing antiepileptic drug such as a barbiturate, carbamazepine, phenytoin or valproate will have a lamotrigine target dose of 200 mg/day. Monotherapy doses of up to 400 mg/day have been evaluated; however, no additional benefit at doses greater than 200 mg/day were observed. For patients not taking the above drugs the following schedule should be followed: weeks 1 and 2: 25 mg/day; weeks 3 and 4: 50 mg/day; week 5:100 mg/day; week 6: 200 mg/day (target dose). If lamotrigine is being added to valproate, the target dose of lamotrigine in combination with valproate is 100 mg/day. Thus the recommended titration schedule is as follows: weeks 1 and 2: 25 mg/every other day; weeks 3 and 4: 25 mg/day; week 5: 50 mg/day; week 6: 100 mg/day (target dose). If lamotrigine is added to one of the above enzyme-inducing drug but not valproate, the following dose titration schedule is recommended: weeks 1 and 2: 50 mg/day; weeks 3 and 4: 100 mg/day (divided doses); week 5:200 mg/day (divided doses); week 6: 300 mg/day (divided doses); and week 7: up to 400 mg/day (divided doses) (target dose) (346).

If patients discontinue concomitant valproate, the dose of lamotrigine should be doubled over a 2-week period in equal weekly increments. For patients discontinuing carbamazepine or other CYP450 enzyme-inducing agents, the dose of lamotrigine should remain constant for the first week and then should be decreased by half over a 2-week period in equal weekly decrements. The dose is then adjusted as needed to the target dose of 200 mg/day. Among patients requiring discontinuation of lamotrigine, the dosage should be decreased by about 50% per week over at least 2 weeks, unless concerns for the patient's safety require a more rapid withdrawal (346).

34.3.4.4. Adverse Effects

Lamotrigine at a dose of 100–400 mg/day appears to be well tolerated, based on two 18-month trials (343, 344). Adverse events reported in at least 10% of one of the treatment groups during the blinded portion of the trials were: headache, (18%), nausea, (14%), infection (13%), insomnia (10%), somnolence (9%), influenza (8%), diarrhea (7%), any rash (6%), dizziness (6%), and tremor (4%). Overall, these ADR occurred no more frequently than placebo. Dizziness was a dose-dependent ADR.

34.3.4.4.1. Dermatologic

Potentially life-threatening rashes, including Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported with lamotrigine therapy. The rashes occur more frequently in children (0.8%) than adults (0.3%). Patients should be instructed to discontinue the drug at the first sign of a rash. Purpura, angioedema, and fixed-drug eruptions are also described. The risk of severe rash may be increased by the co-administration of lamotrigine with valproate, by exceeding the recommended initial dose or escalation periods. Patients experiencing rashes should not be rechallenged with the drug unless the potential benefits of the drug clearly outweigh the risks. The initial dosing guidelines should be adhered to if the patient has been off the drug for a week or more (346).

34.3.5. Oxcarbazepine

34.3.5.1. Mania

Oxcarbazepine, an analog of carbamazepine, has been suggested to have efficacy as a mood-stabilizing agent. Little controlled trial data have been published to suggest that it might be useful in the treatment of patients diagnosed with bipolar disorder. Two small studies have suggested similar efficacy to haloperidol and lithium for acute mania (347). When compared to valproate, the drugs showed equal effectiveness in reducing manic symptoms at the end of a 10-week trial (348). Four 2-week trials in mania have been evaluated. Oxcarbazepine was found to be superior to placebo, similar in efficacy to haloperidol or lithium, and better tolerated than haloperidol in these trials (349). A summary of the usually recommended mood stabilizer doses is presented in Table 34.4.

34.4. Anxiety Disorders

The anxiety disorders included in this discussion are generalized anxiety disorder (GAD), panic disorder (PD), obsessive-compulsive disorder (OCD), post-traumatic stress disorder (PTSD), and social anxiety disorder (SAD). Although diagnostic criteria and symptoms of these disorders differ greatly, many of the same classes of medications are used for their treatment. Specifically, the SSRI medications are effective in treating all the anxiety disorders.

34.4.1. Benzodiazepines

The following benzodiazepines (BZD) have anxiety as an approved indication: chlordiazepoxide (Librium, other names), diazepam (Valium, other names), oxazepam (Serax, other names), clorazepate (Tranxene, other names), lorazepam (Ativan, other names), prazepam (Centrax), halazepam (Paxipam), and alprazolam (Xanax). Five BZD are approved for the management of insomnia: flurazepam (Dalmane, other names), temazepam (Restoril, other names), quazepam (Doral), estazolam (ProSom), and triazolam (Halcion). A given BZD, with the dosage adjusted upward or downward, can serve as both a hypnotic and anxiolytic, respectively (350).

34.4.1.1. Efficacy

34.4.1.1.1. GAD

A review of controlled studies noted numerous problems that make determination of an overall conclusion about BZD efficacy in generalized anxiety disorder (GAD) difficult (351). About 35% of GAD patients treated with BZD experience marked improvement, 40% are moderately improved but still symptomatic, and 25% are unresponsive (351). There is some evidence that BZD are of greater benefit when used to treat patients with moderate to high levels of anxiety (352), in patients with concomitant dysphoria, (353), and in treating somatic symptoms as opposed to the psychic symptoms of GAD (354). Response to BZD may be noted within 1–2 weeks of initiation of treatment. It is estimated that only half of patients with GAD have a return of symptoms after the discontinuation of diazepam after 6, 14, or 22 weeks of treatment (355). Currently, gradual tapering of the BZD after short-term stabilization remains the accepted recommendation by many clinicians (356). Most reviews indicate no significant differences in efficacy among BZD for treatment of GAD or neurotic anxiety, a similar diagnosis that predated GAD (350, 357). Differences in duration of action and metabolism, especially hepatic, may lead to different recommendations regarding which BZD to use in different types of patients with GAD (e.g., the elderly, those with impaired hepatic function) (357).

34.4.1.1.2. Panic Disorder

The results from controlled trials conducted with more than 1700 patients concluded that BZD are effective as antipanic and antiphobic agents when taken regularly and in sufficient doses. Agents investigated in these trials include alprazolam, clonazepam, clorazepate, diazepam, and lorazepam (358–370). Symptoms responding to BZD included anxiety, the frequency and severity of panic attacks, and phobic fear and avoidance. Somatic complaints including cardiovascular, respiratory, gastrointestinal and muscular also responded well (371). Decreases in anticipatory anxiety and disability in work, family life and social life were observed (365, 371). Panic attacks per week decreased by an average of 81%, and the attacks were often eliminated.

In contrast to other drugs, alprazolam proved more effective than buspirone (367), alprazolam and diazepam were more effective than propranolol (363, 372), and alprazolam was equivalent to imipramine (361, 364, 370, 373). Several studies have assessed the combination of a BZD and SSRI (374, 375). The results of these studies have suggested that the combination of a benzodiazepine and an SSRI early in treatment of panic disorder has several possible benefits, including more rapid onset of action and amelioration of SSRI-induced anxiety that is often seen early in treatment. However, little evidence exists for the value of continued combined therapy after 3 to 4 weeks (376). Given the fact that more data exist for SSRI used as monotherapy for long-term treatment of panic disorder, BZD are currently relegated to a second-line option.

Most of the investigations of BZD in panic disorder have focused on short-term outcomes. These studies have shown benefits of treatment within the first week, which is faster than the onset of antidepressants. Uncontrolled reports of long-term treatment with clonazepam (1 year) and alprazolam (2 1/2 years) reported that the drugs maintained their efficacy and were well-tolerated (376). A meta-analysis of treatment of panic disorder concluded BZD maintained effectiveness when used for long-term treatment, but none of the studies cited were controlled (377).

34.4.1.1.3. Social Phobia

BZD are reported to be of limited value in the treatment of social phobia, but this has not been extensively researched (378), and they have been widely used (379). Controlled trials find both alprazolam and clonazepam effective (380, 381) although clonazepam was ineffective when tested against the SSRI, paroxetine (382).

34.4.1.1.4. Obsessive-Compulsive Disorder

Two controlled trials of BZD found clonazepam and alprazolam no more effective than placebo in the treatment of OCD (383, 384).

34.4.1.1.5. Post-traumatic Stress Disorder

A controlled trial found alprazolam producing modest improvement in anxiety symptoms, but not the intrusion or avoidance symptoms of PTSD (385). However, guidelines discourage the use of benzodiazepines for the management of PTSD (556).

34.4.1.2. Dosing

The dose and administration schedule for a BZD in the management of anxiety depends on 1) the clinical presentation; 2) the age, sex, and obesity of the patient; 3) concurrent liver disease; 4) whether the patient smokes; and 5) the pharmacokinetic profile of the BZD. Doses and timing of doses should be titrated for patients based on a balance between efficacy and tolerability (386, 387). A summary of the usually recommended anxiolytic doses is presented in Table 34.5.

Mean or median doses of controlled trials evaluating BZD efficacy in the treatment of GAD were: alprazolam (2 mg/day), chlordiazepoxide (55 mg/day), clorazepate (22 mg/day), diazepam (14 mg/day), and lorazepam (10 mg/day) (351). These doses may be higher than in clinical practice, as they were used in studies investigating maximum short-term benefit. In GAD, diazepam has been shown to be effective in the standard recommended daily dose range of 5–40 mg. The median dose used was 30 mg/day (388). Treatment with alprazolam is initiated with 0.25 or 0.5 mg 2–3 times daily. Dosages may be increased every several days. Most patients require 3–6 mg/day to respond, but 10 mg/day may be required. Duration of initial treatment of

TABLE 34.5 Adult dosages for US available anxiolytics.

Generic name	Trade name	Initial dose (mg/day)	Usual dose range (mg/day)
Benzodiazepines			
Alprazolam	Xanax	0.75	0.75–4
Chlordiazepoxide	Librium	15	15–100
Clonazepam	Klonopin	0.25	0.25–4.0
Diazepam	Valium	4	4–40
Lorazepam	Ativan	2	2–4
Oxazepam	Serax	30	30–120
Non-benzodiazepine			
Chloral hydrate	Somnote	500	500–1000
Buspirone	n/a	15	20–30

GAD is usually recommended for 6 to 24 weeks. Some treating clinicians advise longer-term treatment, as primary or augmenting agents (389–392); others do not agree that this recommendation is compatible with current evidence (356).

Use of benzodiazepines as the primary agent in the initial treatment of panic disorder is not widely recommended. Patients are frequently treated, however, with a combination of a BZD and an antidepressant because of the BZD rapid onset of action in reducing anxiety as well as the anxiety that may be induced by initial doses of SSRI. The mean or median effective doses of the BZD reported in clinical trials of BZD were alprazolam (6 mg/day), chlordiazepoxide (55 mg/day), clorazepate (29 mg/day), diazepam (30 mg/day), lorazepam (4 mg/day), and clonazepam (3 mg/day) (371). These doses reflect an attempt to achieve maximum benefit in the short-run and may be higher than those used in clinical practice. In PD, the recommended daily dose range for diazepam is 5–40 mg with the median effective dose 30 mg/day. Treatment with alprazolam is initiated with 0.25 or 0.5 mg two to three time daily (363). Dosages may be increased every several days. Most patients require 3–6 mg/day for response, but 10 mg/day may be necessary in some patients. Clonazepam has been effective in the majority of patients at a mean dose of 2 mg/day, although some patients require up to 4 mg/day (393, 394). Clonazepam treatment is initiated with 0.5 mg bid.

The duration of action of a single dose of a BZD is determined largely by the volume of distribution and absorption rate of the drug rather than the elimination half-life (395). Diazepam is a very lipid-soluble drug, and is rapidly distributed into fatty tissue. Although its half-life is quite long, the duration of action of a single dose is very short because of high fat solubility which allows it to enter and exit the blood brain barrier quickly. Although lorazepam has a short half-life it may have a longer lasting clinical effect after a single dose than might be expected based on its half-life. A single dose of lorazepam 2.5 mg oral produced significant impairment of psychomotor skills and visual functions related to driving for 24 hours in 10 healthy volunteers (396, 397). In comparison, the impairment in performance after diazepam 10 mg lasted 5–7 hours.

The major distinction to be made for multiple-dose treatment is between drugs with active metabolites and those with no active metabolites. BZD fall into two classes depending upon their biotransformation pathways. One group includes those that are transformed primarily by oxidative pathways to active metabolites. These include chlordiazepoxide, clorazepate, diazepam, halazepam, and prazepam. The half-lives of the parent compound and active metabolites often exceed 48 hours. The other group includes those that are metabolized by conjugation to water-soluble, pharmacologically inactive, glucuronides. These have half-lives that range from 6 to 20 hours and include alprazolam, lorazepam, and oxazepam. BZD with active metabolites will accumulate in the body and not reach steady-state until days or weeks of continuous dosing. Therefore, the full therapeutic or ADR may not be apparent until 5–10 days. For the same reason, clinical effects may persist for several days after the drug is discontinued (396, 397); thus, these drugs may be administered in a once- or twice-a-day schedule (398). BZD with no active metabolites, however, accumulate rapidly and reach steady-state concentrations in 2–4 days. This potential benefit of this class of BZD may be offset by the fact that if the patient misses a dose or a day of treatment, blood concentrations will decline rapidly to zero. This is not so critical with the BZD with active metabolites and long half-life.

Although drug metabolism declines in patients with liver disease, drugs that are transformed by oxidation are affected to a greater extent than those that are conjugated. It is expected that other BZDs metabolized primarily by oxidation, although not specifically studied, would be similarly affected. It is important to remember that because the margin of safety of all BZDs is large, the choice of the particular BZD is not as important as is gradual dose titration and close monitoring (396, 397).

BZDs can produce greater effects on the CNS in the elderly than in younger patients. This is due partly to increased target-organ sensitivity to BZD and partly to changes in drug disposition in the elderly (399). All BZDs, given in repeated doses, will accumulate to some degree and may produce ADR (400). The BZDs with a longer half-life (e.g., diazepam, chlordiazepoxide, clorazepate, prazepam, halazepam) should be prescribed for the elderly in smaller doses (at least 50% of usual dose) and at more widely spaced intervals (once and twice daily versus twice and three times daily) than is recommended for younger patients. The BZDs with a shorter half-life (e.g., oxazepam, lorazepam, alprazolam) also require decreased doses. However, because the pharmacokinetics of these drugs with relatively shorter half-life are not greatly changed in the elderly, the dosage administration schedule can be more similar to that in younger patients.

34.4.1.3. Adverse Effects

BZDs have few pharmacologic effects outside the central nervous system (CNS). The majority of ADR are mediated through the CNS. A wide range of other non-CNS ADR have been attributed to BZD. However, their reported incidence is <1% (401).

34.4.1.3.1. Central Nervous System

Excessive CNS depression (drowsiness, muscle weakness, ataxia, nystagmus, dysarthria) is the most common ADR attributed to BZD. It has been reported in 4–12% of patients taking diazepam or chlordiazepoxide. These ADR are dose dependent and remit when the dose is lowered or the drug discontinued. There is evidence to suggest that the central depressant effects of

BZDs tend to decline as the duration of exposure increases, thereby reducing the sedative effects of chronic exposure and of drug accumulation (401). Elderly individuals and patients with low serum albumin levels are more likely to experience these ADR. The BZD have a risk for abuse and physical dependence (402, 403). The incidence of major abstinence reactions is unknown, although it is thought to be low in comparison with older anxiolytics. Approximately 30% of patients prescribed a BZD for 6 or more weeks will experience withdrawal symptoms upon abrupt discontinuation. Symptoms may be more likely to be severe with higher doses, and in some cases, longer duration of use (404, 405). It is recommended that patients who have been taking BZD regularly for more than 1 month have the drug gradually withdrawn.

The BZDs have been demonstrated in the laboratory to impair reaction time, motor coordination, and intellectual functioning in a dose-related fashion. Fortunately, tolerance develops to these effects (388, 394, 406). The risk of being involved in a traffic accident is increased twofold if a driver is taking a BZD (407–409). The use of ethanol increases this risk of driving impairment. Patients should be cautioned about driving and operating machinery, especially during the first few weeks of treatment (410).

Anterograde amnesia may occur with all BZDs (411). Parenteral administration has been most commonly reported to produce this effect, but it is also reported with oral use. BZDs exert their primary effect in impairing acquisition of new information, but do not appear to affect a person's ability to retain acquired information. The clinical effect of BZDs taken over a long period of time remains to be investigated. However, patients should avoid taking BZD shortly before studying, making important decisions, or performing other tasks dependent on an intact memory.

Like ethanol and barbiturates, BZDs have been reported to produce paradoxical excitement, disinhibition, hostility, rage, and even violent, destructive behavior. These ADRs are infrequent, as well as controversial (410, 412). Triazolam has been associated with a symptom cluster of severe anxiety, agitation, paranoia, hyperacusis, irritability, altered smell and taste, and anger. This reaction is thought to be dose-dependent and occurs more frequently at doses of 0.5 mg or greater (412).

34.4.1.3.2. Respiratory

BZDs are relatively benign as compared to other anxiolytic/hypnotics in their effects on respiration. Even though overdoses with BZDs are frequent, serious sequelae are rare because of minimal respiratory depressant effects. However, in patients with compromised pulmonary function, BZDs may produce clinically significant respiratory depressant effects. All anxiolytic/hypnotics should be used with caution in patients with reduced pulmonary function (410).

34.4.2. Antidepressants

34.4.2.1. Indications

Most of the antidepressant classes marketed have been studied for their potential to treat anxiety disorders.

34.4.2.2. Efficacy

34.4.2.2.1. SSRI and Venlafaxine

GAD

SSRI have been shown to be effective in treating GAD. Paroxetine (20 to 50 mg/day) has been approved by the FDA for the treatment of GAD. Paroxetine responders at 8 weeks have lower relapse risk when continued on paroxetine for 24 weeks (413–416). Sertraline 50 mg/day and escitalopram are similarly effective (417, 418). Venlafaxine extended release has also been FDA-indicated for the short-term (8-week) and long-term (24-week) treatment of GAD (419, 420).

Panic Disorder

A recent meta-analysis questioned the superiority of SSRIs to other antidepressants when it found effect sizes of other antidepressants equivalent to the effect sizes of SSRIs in acute treatment of panic disorder (421). Paroxetine was the first SSRI to be FDA-indicated for panic disorder, based on large multi-center controlled studies. Paroxetine has been efficacious in patients with and without agoraphobia. Benefit was shown within 4 weeks and efficacy in reducing panic symptoms was maintained for up to 48 weeks. Paroxetine has demonstrated superior efficacy to clomipramine. Efficacy occurred more often at 40 mg than lower doses (389, 422–424). Fluoxetine 20 mg/day, sertraline 125 mg/day, citalopram 20–30 mg/day and venlafaxine are also effective (425–430).

Social Anxiety Disorder or Social Phobia
Sertraline and paroxetine are both FDA-indicated for the treatment of social anxiety disorder. Paroxetine has been studied more than the other SSRI agents have. The response rate ranged from 55% and 66% (431, 432). Escitalopram, fluvoxamine and venlafaxine have also been found effective (433–437). Buproprion and maprotiline were ineffective (438, 439).

Post-traumatic Stress Disorder
Agents in the SSRI and serotonin-norepinephrine reuptake inhibitors (SNRI) classes have been studied to various degrees. At this time, sertraline (440–442) and paroxetine (443, 444) are the sole SSRI that have been FDA-indicated for the treatment of PTSD. The studies noted improvement in all PTSD symptom clusters (intrusive recollections, avoidant/numbing symptoms, and hyper-arousal), though effect sizes were modest (sertraline: 0.3–0.4 and paroxetine: 0.5), and higher doses did not show additional benefit as compared to lower doses. Vietnam combat veterans did not show benefit, (445). Additionally, controlled trials have shown positive effects for fluoxetine in the treatment of PTSD (446–448). The results of follow-up studies suggest the need to continue sertraline for at least a year in responders (441).

34.4.2.2.2. Tricyclic Antidepressants

GAD
A meta-analysis focusing on controlled studies of antidepressants used in GAD concluded that imipramine, paroxetine, and venlafaxine are effective. This meta-analysis also indicated that imipramine and paroxetine, when compared to each other are of equivalent value (354). The direct comparison of the TCA and BZD classes resulted in the implication that alprazolam was primarily effective in treating the somatic symptoms of GAD, while imipramine predominantly affected the psychic component (388).

Panic Disorder
The use of TCAs in panic disorder with or without agoraphobia has been evaluated in 11 controlled trials with 1,633 patients (358, 370, 449–455). Imipramine and clomipramine were shown to be effective in the treatment of panic attacks with or without agoraphobia.

Social Phobia
Clomipramine is effective in the treatment of social phobia (dose range 25 mg to 225 mg/day) in four studies (456–458).

Post-traumatic Stress Disorder
One small study with amitriptyline, and one small study with imipramine, found TCAs to have modest effects on PTSD symptoms on veterans (459, 460). A four-week trial of desipramine, however, did not demonstrate an effect on symptoms of PTSD. None of the TCAs alleviated avoidance and numbing symptoms, (445, 461).

34.4.2.2.3. Monoamine Oxidase Inhibitors

The pharmacologic management of panic disorder and agoraphobia with panic attacks was originally investigated in the early sixties with MAOIs and with TCAs (378, 462, 463).

Panic Disorder
Controlled trials (five with phenelzine) concluded that MAOI are effective in between 65% and 70% of patients with panic disorder (454, 465–467). The overall response rate with MAOI was slightly less than for TCA, but this may have been to limitations such as low doses of MAOI used, small sample sizes, and mixed groups of patients. MAOI are rarely used due to the dietary restrictions and the potential for drug-drug interactions

Social Phobia
Four controlled trials were undertaken to investigate the possible role of phenelzine in social phobia (380, 468–470). Despite the positive results mentioned previously, MAOI are not recommended as first-line treatment options due to the reasons listed previously.

Post-traumatic Stress Disorder
Two controlled trials found the MAOI effective in an 8-week trial but not a 4-week (460, 471).

If an adequate trial with one treatment (e.g., antidepressant, BZD) fails, then another treatment should be tried. Though not well studied, combination treatment with various agents has been reported to succeed when individual drugs fail (464).

34.4.2.3. Dosing

The time to response was 2–6 weeks, although some patients may take longer to respond. Duration of antidepressant treatment in a newly diagnosed patient may be 1 year. Attempts to discontinue the drug should be attempted periodically to determine continuing need (463). Several reports have indicated that, although some patients may respond to imipramine doses of 25 mg/day, most patients require >150 mg/day to achieve a satisfactory response. Some patients may require that the dose be increased to 400 mg/day (463). Imipramine doses should be initiated at 10–25 mg/day, which can be increased to 100–200 mg/day over a 2- to 4-week period. If a response is not seen in 2–6 weeks, the dose may be increased to 400 mg/day. Doses of antidepressants other than imipramine in the management of panic disorder are typically in the antidepressant range.

Usually patients with anxiety disorders tend to improve for up to 6–12 months with pharmacologic management (455). Therefore, after 6–12 months of successful treatment, it is reasonable to consider discontinuing medications (472). However, regardless if the patient has been successfully treated, approximately 50–95% of patients will relapse (473).

It is recommended that any of the three classes (e.g., BZD, TCA, MAOI) of treatment be tapered gradually over 1 to 3 months to allow early detection of relapse. Tapering of BZD should be done very slowly to avoid significant withdrawal symptoms, especially if higher doses are being used (472). If the patient relapses after the first taper, then reinstitution of treatment often achieves clinical control. It is recommended that tapering be tried again in 3–6 months.

34.4.2.4. Adverse Effects

(See antidepressant adverse effects).

34.4.3. Buspirone

34.4.3.1. Efficacy

Buspirone is the first non-BZD anxiolytic to be introduced in the U.S. The drug is not a controlled substance. It is only indicated for the short-term treatment of GAD, when symptoms are rated as mild to moderate in severity (474, 475). However, the drug has not been found to be effective in the treatment of PD (368, 476).

34.4.3.2. Dosing

The usual anxiolytic dose is 15–45 mg/day. The initial starting dose is 15 mg/day divided 2–3 times per day. The dose may be increased by 5 mg/day and the maximum recommended daily dose is 60 mg (475). A summary of the usually recommended anxiolytic doses is presented in Table 34.5.

34.4.3.3. Adverse Effects

All reviews of the overall ADR profile of buspirone have concluded that the drug (45%) has more ADR than placebo (33%) but fewer than the BZD (45–60%) (477).

Dizziness, drowsiness, and headache occurred in 12, 10, and 6% of buspirone-treated patients, respectively. These ADR are more common with doses >20 mg/day. Dizziness was reported to occur 30–60 minutes after buspirone was administered, especially when subjects were walking or standing.

Dysphoria has been reported, primarily with doses >30 mg/day. Initial studies indicated that buspirone <20 mg/day produced less psychomotor impairment than the BZD. Buspirone in combination with ethanol results in less psychomotor impairment than lorazepam or diazepam plus ethanol (478–480). Studies of the abuse potential of buspirone in animals and recreational sedative users demonstrated no overt sedative or euphoric effects (474, 475). It is important to note that buspirone is not cross-tolerant with standard anxiolytic/hypnotics (i.e., BZD, barbiturates). Therefore, buspirone will not prevent withdrawal signs and symptoms that may occur if a patient is abruptly changed from one of these drugs to buspirone. Likewise, buspirone will not treat anxiolytic-hypnotic withdrawal symptoms.

34.4.4. Beta-Adrenergic Blocking Drugs

34.4.4.1. Efficacy

Of the beta-adrenergic receptor blocking agents available in the US, propranolol is the most extensively studied in the management of anxiety. It is not approved by the Food and Drug Administration (FDA) for use as an anxiolytic.

The anxiolytic effect of propranolol was first examined in 1966. The majority of six controlled studies show propranolol to be only slightly more effective than placebo in the treatment of GAD (481). According to most studies, propranolol produces the greatest improvement in patients with primarily somatic complaints (e.g., palpitations, tremor, sweating); psychological symptoms (e.g., apprehension, irritability, tension) respond less well. Most published studies reported BZD to be superior to propranolol in anxiety disorders (363, 463).

Beta-blockers appear to be effective in the treatment of acute situational anxiety (481). The drugs appear to be most effective when somatic symptoms predominate (482). Beta-blockers have improved performance in students taking examinations, decreased tachycardia and other responses associated with the stresses of race car driving, decreased somatic symptoms during the stress induced by public speaking, reduced tremor in string instrument players, and reduced symptoms of anxiety related to stress in anxious outpatients (481).

34.4.4.2. Dosing

Propranolol 40–80 mg has been used successfully in acute situational anxiety and for social phobia (378). The dose should be administered 1–2 hours prior to the stressful event.

34.5. Obsessive-Compulsive Disorder

Most of the medications shown to have efficacy in obsessive-compulsive disorder are serotonin agonists. With current treatment options, a 10 week course of drug treatment will generally result in 40–60% of the OCD patients experiencing approximately a 20–35% decrease in their obsessions and compulsions as measured by the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) (483). The SSRI antidepressants, as well as the TCA clomipramine have been shown to have efficacy for the short-term treatment of OCD. The increase in the improvement rate over placebo was greater for clomipramine than the SSRI. Patients are usually initiated with a SSRI. Due to the ADR profile of clomipramine, the medication is usually reserved for those failing several trials of SSRI, despite the fact that clomipramine is sometimes suggested to have some superiority over SSRI. Finally, the presence or absence of depressive symptoms does not confound the effectiveness of clomipramine and the SSRI in the treatment of OCD (484).

34.5.1. SSRI/Venlafaxine

Controlled trials have demonstrated the effectiveness of fluoxetine, fluvoxamine, sertraline, paroxetine, and citalopram in OCD (484–486). Sertraline and paroxetine have shown sustained improvement for 18 months (383, 487). Venlafaxine has proven itself effective in a short-term study (488). Studies suggest that higher doses of SSRI are required for effective treatment of OCD compared to treatment of major depressive disorder. For example, both paroxetine and fluoxetine had to given at 40 mg or 60 mg and were ineffective at lower doses in some but not all studies (485). Small studies requiring replication suggest the benefit of antipsychotic augmentation of SSRI in the treatment of OCD unresponsive to SSRI monotherapy. A review of OCD studies concluded that clomipramine may have greater anti-obsessional effects than SSRI and that despite the usual recommendation that it be used only if SSRI fail, it should be considered a first-line agent and used with initially low and then gradually increasing doses (489).

34.5.2. TCA (Clomipramine).

The potent serotonin agonist, clomipramine is effective in the treatment of OCD whereas the less potent serotonin agonist TCA, nortriptyline, amitriptyline, and imipramine have not been shown to be effective (490–497). At least 23 trials have documented the effectiveness of clomipramine in the treatment of OCD in both adults and children (484, 485). A large multi-center trial showed a 40% reduction in OCD symptom ratings in patients treated with clomipramine compared to a minimal reduction in symptoms for patients treated with placebo (498).

34.5.2.1. Efficacy

Clomipramine is a specific serotonin reuptake blocker, although its metabolite, desmethylclomipramine has effects on blocking norepinephrine reuptake.

34.5.2.2. Dosing

The initial dose is clomipramine 25 mg/day administered as a single dose at bedtime. The dose should be gradually increased over several days to two weeks as determined by side effects to a minimum dose of 150 mg/day. Patients who show no response to 150 mg/day after four weeks of treatment should have their dose increased to 200 mg/day. If there is little or no improvement to this dose within the next two or three weeks, the dose should be increased to 250 mg/day. Some response of OCD symptoms to clomipramine may be noticed during the first several weeks of treatment, but often the maximal response occurs after 6 to 12 weeks. Some patients continue to show further gradual improvement for months after treatment initiation.

34.5.2.3. Adverse Effects

Clomipramine side effects are similar in severity and nature to those of tricyclic antidepressants such as amitriptyline. Side effects include drowsiness, orthostatic hypotension, tremor, lethargy, fatigue, impaired cognition, weight gain, and a variety of anticholinergic effects such as dry mouth, constipation, and blurred vision. Sexual changes associated with clomipramine use include decreased sexual interest and anorgasmia. One report found 22 of 24 OCD patients (male and female) developed anorgasmia, usually within the first few days of clomipramine initiation (499).

34.6. Dementia

34.6.1. Cholinergic Agonists

Alzheimer's Dementia is thought to be associated with loss of cholinergic neurons in the brain. Therefore, most of the treatment options developed have focused on manipulation of the cholinergic system (172, 500). Anticholinesterases (acetylcholinesterase inhibitors) inhibit acetylcholinesterase in the synaptic cleft, thereby leading to an increase in cholinergic synaptic transmission. These agents are classified by their selectivity for different cholinesterase enzymes and by their reversibility for inhibition of acetylcholinesterase. The four currently available agents include tacrine, donepezil, rivastigmine, and galantamine.

34.6.1.1. Tacrine

Tacrine produced a mean 4 to 6% advantage over placebo in studies of patients greater than 6 months in duration. Tacrine requires four times daily dosing. In the clinical trials, 55% of patients with mild to moderate dementia, Alzheimer's type (DAT) dropped out of the studies because of ADR, that were mostly elevations in hepatic enzymes. Due to the high risk of significantly elevated liver function tests, serum transaminase levels should be performed every other week from at least week 4 to week 16, and then every 3 months thereafter.

34.6.1.2. Donepezil

Studies of patients with mild to moderate DAT showed that donepezil produced a 4–6% improvement in cognitive and global change scales when compared to placebo (501, 502). Frequently reported ADR were mainly GI-related, but insomnia was also reported in 14% of patients. A retrospective study using double blind controlled data showed a significant behavioral improvement in 41% of patients treated with donepezil (503). A long-term follow-up study demonstrated safety and efficacy of donepezil for treatment up to 144 weeks in patients with moderate to moderately severe DAT (504). Donepezil was shown to decrease caregiver time as well as lower the level of caregiver stress due to the slowing decline of activities of daily living (ADL) in patients with moderate to severe AD in a 24-week controlled trial of donepezil (505). Finally, patients with moderate to severe DAT given donepezil for 24 weeks demonstrated improvements in global, cognitive function and behavioral measures (506). Donepezil is available as 5, 10, and 23 mg tablets. Dosing should start at 5 mg daily, and target dose is 5–10 mg/day. For patients with moderate to severe Alzheimer's disease the dosage may be increased to 23 mg daily after three months of treatment. The most common adverse reactions reported include nausea, diarrhea, vomiting, muscle cramps, fatigue, and anorexia.

34.6.1.3. Rivastigmine

Rivastigmine, marketed in 2000 for the treatment of AD, is administered once daily. Two controlled trials showed rivastigmine produced 25–30% improvements in scores on neuropsychological tests and measures of behavior (507, 508). Improvements were greater than placebo, but the mini-mental status examination (MMSE) did not change significantly, and clinical gains were modest. Twenty percent of patients could not tolerate 6–12 mg daily due to cholinergic ADR. Rivastigmine should be initiated at 1.5 mg twice daily, and may be increased every two weeks to a maximum of 6 mg twice daily. Most common ADR include nausea (47%), vomiting (31%), anorexia (17%), and weight loss (18%–26%).

34.6.1.4. Galantamine

Galantamine is an acetylcholinesterase inhibitor that also acts as a modulator at nicotinic cholinergic receptor sites. A controlled trial of patients with DAT given placebo or 18, 24, or 36 mg/day galantamine for 3-months, patients treated with 24 mg/daily had better cognitive outcomes than placebo. ADR similar to the other cholinesterase inhibitors were well-tolerated at the 18 and 24 mg/day doses (509). Galantamine should be initiated at 4 mg twice daily, and may be gradually increased to a total of 16–24 mg/day administered as twice daily dosing. Adverse reactions include nausea, vomiting, anorexia, diarrhea, dizziness, and headache. Administering this agent with food may decrease ADR.

34.6.2. NMDA Receptor Antagonists

34.6.2.1. Memantine

Like donepezil, memantine, a NMDA glutamate receptor antagonist, is also indicated for the treatment of moderate to severe DAT patients. Patients treated with 20 mg/day memantine were three times more likely to remain independent with ADL function (510). Additionally, the drug has been proven to save care-giver time, improve cognition, ADL, global outcome, and behavior when memantine was added (511). Memantine should be initiated at 5 mg daily, with a target of 20 mg daily achieved by increasing dose by 5 mg increments no more quickly than weekly. ADR reported include dizziness, and headache; there were low occurrences of adverse events similar to placebo except for infrequent events.

34.7. Anti-Aggression

There are no drugs available currently that produce improvement in the memory dysfunction of patients with dementia. Thus, the pharmacotherapy of dementia is primarily targeted at improving behavior. Agitation is a common presentation in patients with dementia. Patients sometimes display violent outbursts in addition to wandering, screaming, and other behavioral issues. Pharmacological interventions have focused on antipsychotic medications. Although a meta-analysis has showed the benefits of these agents are superior to placebo, the overall benefits were modest (84). Antipsychotics have recently been investigated for possible association with increased cerebrovascular events or death in elderly patients with dementia. Although more data are needed to fully elucidate this matter, the use of antipsychotics in patients with dementia who are acutely agitated should be assessed on a risk-benefit analysis. Other medications have been investigated, with varying outcomes, for the treatment of agitation in dementia: gabapentin, carbamazepine, divalproex, and other mood stabilizers have all been investigated (512–516).

34.8. Hypnotics

When behavioral methods fail or cannot be applied for the treatment of insomnia, hypnotics may be indicated. Pharmacological treatment of insomnia is effective for brief therapy of transient insomnia (517). Hypnotics may be used as adjunctive treatments or on an as needed basis for the treatment of chronic insomnia (518). If hypnotics are used on a long-term basis, the prescribing physician should closely monitor the patient's continuing need for medication. Vigilant monitoring is required because of the potentially adverse effects of many of hypnotics, including addiction, tolerance, withdrawal, impaired cognition, and impaired motor function leading to increased potential for falls and motor vehicle accidents (519).

The benzodiazepine receptor agonists (BZRA) marketed as hypnotics (e.g., flurazepam, temazepam, quazepam, estazolam, eszopiclone, triazolam, zolpidem, and zaleplon) are the most useful hypnotics available to the clinician. The term BZRA refers to benzodiazepines (BZD) in addition to the three newest hypnotics (zolpidem, zaleplon, and eszopiclone). Zolpidem, zaleplon,

TABLE 34.6 Adult dosages for US available hypnotics.

Generic name	Trade name	Initial dose (mg/day)	Usual dose range (mg/day)
Benzodiazepines			
Estazolam	ProSom	1	1–2
Flurazepam	Dalmane	15	15–30
Quazepam	Doral	7.5	7.5–15
Temazepam	Restoril	7.5*	7.5–30*
Triazolam	Halcion	0.125	0.125–0.25
Non-benzodiazepine benzodiazepine receptor agonists			
Eszopiclone	Lunesta	1	1–3
Zaleplon	Sonata	5	5–20
Zolpidem	Ambien	5	5–10
Melatonin receptor agonists			
Ramelteon	Rozerem	8	8
Orexin receptor antagonist			
Suvorexant*	Belsomra®	5	5–20
Tricyclic antidepressant			
Doxepin	Silenor	3	3–6

*Editor suggested information.

and eszopiclone are not benzodiazepines by chemical structure (zolpidem is an imidazopyridine, zaleplon a pyrazolopyrimidine, and eszopiclone a pyrrolopyrazine) but are pharmacologically active at the benzodiazepine receptor. Ramelteon, a melatonin receptor agonist, is hypothesized to be more effective than melatonin for sleep.

All the BZD are associated with episodes of anterograde amnesia. Thus, patients should be counseled to use the lowest effective dose and go to sleep as soon as possible after taking the drug. Physiological and psychological dependence are a potential problem primarily in patients with concomitant substance abuse diagnoses. Because of the risk of depressing the respiratory drive, BZD should be used with caution in patients with sleep apnea (519). Abuse and dependence problems have been associated with both zolpidem and zaleplon with the former drug causing the most problems during the first night of abrupt withdrawal. Zaleplon is rapidly absorbed except following a high fat content meal. Because of its short duration of action, it can be used as late as 4 hours prior to waking. Eszopiclone is a stereoisomer of the hypnotic zopiclone, which has been available in Europe since 1992 (520). Ramelteon is not a controlled substance and has been shown continuously effective for up to 35 nights. It does not appear to produce residual effects, rebound insomnia, or symptoms of withdrawal with prolonged use. It has been shown to be effective in elderly patients with questionable effectiveness in patients under 65 years old (521).

Other agents used as hypnotics include doxepin and trazodone. Both agents are antidepressants that have clinical utility in treating patients with insomnia. Neither drug has the abuse potential that the BZRA display. Therefore, they may be utilized in patients who need treatment for insomnia and also have a substance use disorder.

A summary of the usually recommended hypnotic doses is presented in Table 34.6.

34.9. Stimulants

Stimulants are often utilized for the management of attention deficit hyperactivity disorder (ADHD) and narcolepsy (Table 34.7). Other stimulants such as modafinil is utilized for narcolepsy, sleep apnea, and shift work sleep disorder. Occasionally these agents are used off label to treat depression in the medically ill or those with terminal illness.

Stimulants are commonly associated with headache, deceased appetite, abdominal pain and nausea. If doses are given too late in the day, patients may have insomnia. Caution should be observed in patients with cardiovascular disease as stimulants may cause hypertension, tachycardia and palpitations. Other side effects include dry mouth, nervousness, restlessness, anxiety and dizziness.

TABLE 34.7 Stimulants.

Generic name	Trade name	Initial dose (mg/day)	Usual dose range (mg/day)
Dexmethylphenidate	Focalin	5	2.5–20
Dextroamphetamine and amphetamine	Adderall	5	2.5–40
Dextroamphetamine	Dexedrine	5	2.5–40
Methylphenidate	Ritalin	5	2.5–90
Methylphenidate extended release	Concerta	18	18–54
Atomoxetine	Strattera	40	40–80
Modafinil	Provigil	200	200–400

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35
Cognitive and Behavioral Therapies

Edward S. Friedman, M.D., Aaron M. Koenig, M.D., and Michael E. Thase, M.D.

Abstract For more than 40 years, the cognitive and behavioral therapies have evolved as alternatives to more traditional non-directive and insight-oriented models of psychotherapy (1). Cognitive and behavioral therapies now include a diverse group of interventions that share several pragmatic and theoretical assumptions. First, there is an emphasis on psychoeducation—patients are assumed to be capable of learning about their disorder and the interventions they will need to treat it. Second, homework and self-help assignments are usually recommended, to provide patients with the opportunity to practice therapeutic skills and generalize positive behaviors outside of the therapy session. Third, treatment is based on the objective assessment of psychiatric symptoms, and the selection of therapeutic strategies derives logically from such assessments. Fourth, therapeutic tools are generally structured, directive, and characterized by a high level of therapist activity, and for most disorders they are time-limited in nature. Finally, these therapies are based on empirical evidence that validates and guides the choice of therapeutic techniques.

Keywords Psychotherapy • Cognitive • Behavioral • Learning theory • Psychoeducation

35.1. Cognitive Model

The proposition that cognition is the primary determinant of emotion and behavior dates to the writings of the Greek Stoic philosophers (2), but in modern times the work of Aaron T. Beck has been the greatest impetus for the development of cognitive therapy (1, 3–6). [*For an excellent review of the history of CBT, see Dobson and Block* (2) *and Clark, Beck, and Alford* (7)*, which also review the philosophical and theoretical assumptions of the cognitive model.*] Contributions from cognitive psychologists, behavioral therapists, and other clinical practitioners have subsequently been incorporated into the cognitive model (8), and together they form the current practice of "cognitive behavioral therapy" or CBT.

In the 1960s, as Beck began to formulate his theories, Freud's psychoanalysis was the predominant therapeutic treatment approach. Freud conceived of depression as resulting from anger turned inward (9). Beck, however, could not find evidence for this hypothesis, and instead observed stereotypical patterns of pessimism, self-criticism, and distorted information processing in depressed patients (3). This early work led to the development of a cognitive model of depression (4), the description of

E.S. Friedman, M.D.
Associate Professor, Department of Psychiatry, University of Pittsburgh Medical Center,
Western Psychiatric Institute Clinic, Pittsburgh, PA, USA
e-mail: friedmane@upmc.edu

A.M. Koenig, M.D. (✉)
Resident, Department of Psychiatry, University of Pittsburgh Medical Center, Pittsburgh, PA, USA
e-mail: koenigam@upmc.edu

M.E. Thase, M.D.
Professor, Department of Psychiatry, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, USA
e-mail: thase@mail.med.upenn.edu

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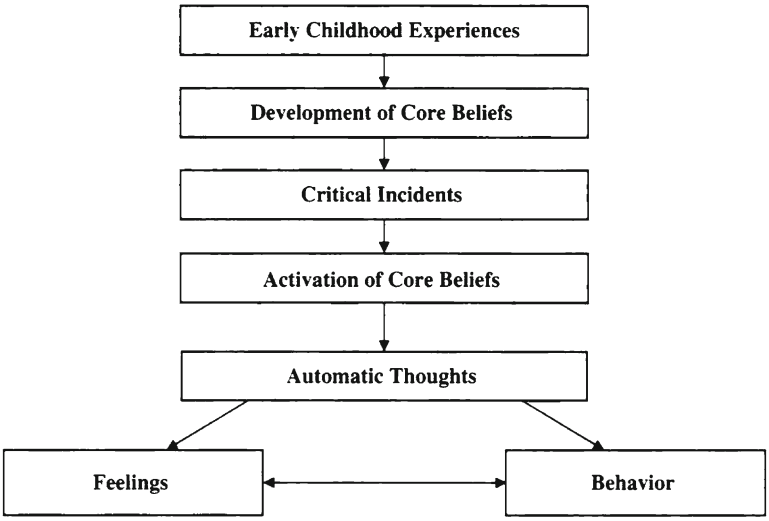

FIGURE 35.1 The cognitive model–cognitive case conceptualization.

specific treatment interventions, and a substantial research effort designed to study cognitive functioning and treatment outcomes in a variety of disorders (8, 10).

Figure 35.1 depicts a simplified model for understanding the relationships between environmental events, cognitions, emotion, and behavior. This model posits that the perception of environmental stress initiates cognitive processes that are associated with physiological and affective arousal. These emotions, in turn, have a potent reciprocal effect on cognitive content and information processing. In depression, cascades of dysfunctional thoughts and activation of emotion can subsequently occur, as highlighted in Fig. 35.2. An individual's behavioral response to stimuli and thoughts are viewed as both a product and a cause of maladaptive cognitions, and thus treatment interventions may be targeted at any or all components of the cognitive model.

Of course, many other factors are involved in the development and propagation of psychiatric disorders, including genetic predisposition, state-dependent neurobiological changes, and various interpersonal variables. These influences are also included in the case conceptualization in CBT. Wright and Thase (11) have outlined an expanded cognitive-biological model that can be used to synthesize cognitive and neurobiological factors in a combined treatment approach. Contemporary psychiatric research is striving to understand how best to combine and/or sequence CBT and pharmacotherapy, as well as understand CBT technique in the context of ongoing discoveries in the field of cognitive neuroscience. Despite ongoing developments, the working model in Fig. 35.1 can be used as a practical template to guide the therapist's case formulation and intervention.

35.1.1. Automatic Thoughts and Schemas

The CBT model conceptualizes many psychiatric disorders as the result of dysfunctional information processing at two major levels of cognition: the usually fleeting, automatic negative thoughts (ANTs) and schemas (cognitive structures within the mind, the specific content of which are core beliefs), the latter of which are more persistent and relatively stable cognitive-behavioral interactions and patterns (4, 6, 12, 13). Automatic negative thoughts are stream-of-consciousness thoughts that arise spontaneously or in response to prompts or stimuli. Affective shifts are generally accompanied by automatic negative thoughts (14), and in many cases ANTs are directly triggered by affective arousals (such as anger, anxiety, or sadness). ANTs enter into awareness and are generally accepted as having emotional validity (i.e. believable). While we all experience automatic thoughts, ANTs in depression, anxiety, and other psychiatric disorders are distinguished by their greater intensity and frequency. LeFebvre (15) and Beck (5) coined the term "cognitive triad" to describe the content areas of automatic negative thoughts. Typically, ANTs are about one's self, one's world (including significant others or people in general), and one's future. For CBT practitioners, the thematic content of automatic negative thoughts are used to reveal deeper levels of cognition, including beliefs, rules, and schemas. Patients can be taught to examine their beliefs and the operational rules that produce them, and although patients are not fully aware of their schemas, such cognitions are usually accessible through questioning techniques used in CBT (16).

Beck and colleagues (10) have noted that stereotypic errors in logic (termed cognitive errors or cognitive distortions) also shape the content of automatic thoughts. Examples and descriptions of common cognitive distortions are listed in Table 35.1.

DYSFUNCTIONAL THOUGHT RECORD				
Situation	Feeling	Automatic Negative Thought (ANT)	Cognitive Distortion (CD)	Realistic Alternative (ANT-CD)
Cathy could not "admit" to her parents that she was depressed. Her mother is a strict fundamental Christian who does not "believe in therapy." Her father has a passive personality style.	*Uneasy* *Anxious* *Sad* *Ashamed* *Frustrated* *Helpless*	I am a failure.	All or none	Although I am afraid of my mother's reaction, I am often successful in things I do.
		I have a poor character.	Emotional Reasoning	Just because I'm feeling sad and ashamed doesn't prove I have a poor character.
		I am not a good person if mother disapproves.	Mind-reading	I have assumed my mother will be disappointed in me but I don't know this for certain.
		I do not deserve good things.	Personal-ization	There is no evidence, other than my feeling so, that I am not worthwhile. I deserve good things as much as anyone.

Summary	Evidence for ANT "I am a failure"	
	+	-
Although I am afraid of my mother's reaction, the fact that I am doing therapy does not mean I am a failure and a deficient person. I will tell my parents and see what they actually say.	I cannot talk to my parents.	I am a good schoolteacher. My friends like me. I have most often succeeded in things I attempt.

FIGURE 35.2 Example of dysfunctional thought record.

TABLE 35.1 Common patterns of irrational thinking in anxiety and depression.

Cognitive error	Definition
Overgeneralization	Evidence is drawn from one experience or a small set of experiences that reach an unwarranted conclusion with far-reaching implications
Catastrophic thinking	An extreme example of overgeneralization, in which the impact of a clearly negative event or experience is amplified to extreme proportions, e.g., "If I have a panic attack, I will lose all control and go crazy (or die)"
Maximizing and minimizing	The tendency to exaggerate negative experiences and minimize positive experiences in one's activities and interpersonal relationships
All-or-none thinking (black or white, absolutistic)	An unnecessary division of complex or continuous outcomes into polarized extremes, e.g., "Either I am a success at this, or I'm a total failure"
Jumping to conclusions	Use of pessimism or earlier experiences of failure to prematurely or inappropriately predict failure in a new situation; also known as fortune telling
Personalization	Interpretation of an event, situation, or behavior as salient or personally indicative of a negative aspect of self
Selective negative focus ("ignoring the evidence" or "mental filter")	Undesirable or negative events, memories, or implications are focused on at the expense of recalling or identifying other, more neutral or positive information; in fact, positive information may be ignored or disqualified as irrelevant, atypical, or trivial

Adapted from Beck AT, Rush AJ, Shaw BF, Emery G. Cognitive Therapy of Depression. New York: Guilford Press, 1979. Reprinted with permission from Guilford Press.

Cognitive errors help to translate between the "surface" level of cognition (revealed in automatic negative thoughts) and deeper cognitive structures such as basic assumptions, rules, and schemas. It has been proposed that apparently "illogical" thinking during times of heightened emotion may have had evolutionary value (17). Specifically, cognitive distortions during periods of affective arousal tend to narrow one's focus of attention, simplify information processing, and intensify behavioral responses—ultimately allowing an individual to respond decisively to threats. This is consistent with recent findings that elucidate the neurocircuitry of brain fear pathways (distinct affective and cognitive pathways). LeDoux has shown that activation of the fear pathway causes a sequential activation of affective (limbic-amygdala branch) and cognitive (hippocampal-cortical branch) pathways. The affective pathway is shorter, however, allowing activation to occur milliseconds before the cognitive pathway. This primes the system with a sequenced affective/cognitive response to fearful environmental stimuli (18).

Schemas are relatively stable cognitive patterns that are the result of one's beliefs and attitudes. Such basic beliefs and attitudes lie behind assumptions (unspoken rules) that act as templates for screening and interpreting information from the environment. Psychological well-being results from an adaptive cognitive pattern that 1) yields realistic appraisals of one's ability to be trusting and to love and 2) produces realistic expectations regarding one's adequacy in different situations and endeavors. Although unspoken, schemas may be inferred from beliefs and attitudes. In the cognitive model, dysfunctional attitudes are the structural "bridge" between pathological schemas and automatic negative thoughts. Schemas pertaining to safety, trust, vulnerability to threat, self-evaluation, as well as ability to love and be loved, provide a framework for understanding an individual's reaction to stressful stimuli, and provide a means of understanding disorders such as anxiety, depression, or characterological disturbances (19, 20). A number of schemas relevant to psychiatric illness are listed in Table 35.2.

Most psychopathological schemas are developed early in life, when the individual is relatively powerless and dependent on caregivers (21). The cognitive model of psychiatric illness emphasizes the concept of stress-diathesis (17, 22). From this perspective, someone who experienced a lack of parental love as a child might employ the rule: "If I am loved by others, then I am

TABLE 35.2 Proposed maladaptive schemas.

Autonomy	
Dependence	The belief that one is unable to function without the constant support of others
Subjugation-lack of individuation	The voluntary or involuntary sacrifice of one's own needs to satisfy others' needs
Vulnerability to harm or illness	The fear that disaster (i.e., natural, criminal, medical, or financial) is about to strike at any time
Fear of losing self-control	The fear that one will involuntarily lose control of one's own impulses, behavior, emotions, mind, and so on
Connectedness	
Emotional Deprivation	The expectation that one's needs for nurturance, empathy, or affect will never be adequately met by others
Abandonment-loss	The fear that one will imminently lose significant others or be emotionally isolated forever
Mistrust	The expectation that others will hurt, abuse, cheat, lie, or manipulate you
Social isolation, alienation	The belief that one is isolated from the rest of the world, is different from other people, or does not belong to any group or community
Worthiness	
Defectiveness-unlovability	The assumption that one is inwardly defective or that, if the flaw is exposed, one is fundamentally unlovable
Social undesirability	The belief that one is outwardly undesirable to others (e.g., ugly, sexually undesirable, low in status, dull, or boring)
Incompetence-failure	The assumption that one cannot perform competently in areas of achievement, daily responsibilities, or decision-making
Guilt-punishment	The conclusion that one is morally bad or irresponsible and deserving of criticism or punishment
Shame-embarrassment	Recurrent feelings of shame or self-consciousness experienced because one believes that one's inadequacies (as reflected in the preceding maladaptive schemas of worthiness) are totally unacceptable to others
Limits and standards	
Unrelenting standards	The relentless striving to meet extremely high expectation of oneself at all costs (i.e., at the expense of happiness, pleasure, health, or satisfactory relationships)
Entitlement	Insistence that one should be able to do, say, or have whatever one wants immediately

From Thase ME, Beck AT: An overview of cognitive therapy. In Wright JH, Thase ME, Beck AT, Ludgate JW (eds): Cognitive Therapy with Inpatients: Developing a Cognitive Milieu. New York: Guilford Press, 1993:9. With permission from Guilford Press. Adapted from Young J: Schema-focused cognitive therapy for personality disorders. Unpublished manuscript, Cognitive Therapy Center of New York, 1987.

worthwhile." This rule might remain latent until activated by a life stressor, such as a romantic breakup. In such a situation, the vulnerable person experiences considerable emotional turmoil, whereas someone with a more resilient self-schema might be more confident in their likelihood of establishing another relationship in the future, and thus may only experience a limited period of sadness (23). Some schemas may also be influenced by neurobiological factors. In panic disorder, exquisite sensitivity to neurobiological signals, such as the "suffocation alarm," may simultaneously trigger noradrenergic arousal and fearful cognitions (24). Past experiences of panic can reinforce the rule "I am weak and unable to cope with distress," triggering further arousal and avoidance of stressors. In recurrent depression, neurobiological changes may exaggerate stress responsivity and undermine the individual's hardiness in the face of adversity, thus dampening hedonic capacity (11). As a consequence, the individual may develop the dysfunctional attitude "I am powerless to change my destiny," which expresses helplessness and hopelessness, negative core beliefs that are reinforced by the chronic depressive state.

In general, studies of individuals suffering from depression and anxiety have confirmed pathological information processing. Automatic negative thoughts and cognitive errors are more common in depressed patients than in control subjects. Similarly, automatic thoughts concerning lack of control, threat, or danger have been documented in patients with high levels of anxiety. In clinical studies, depressed subjects have demonstrated elevated levels of dysfunctional attitudes, distorted attributions to negative life events, and negatively biased responses to feedback. Anxious individuals frequently have an unrealistic view, an attentional bias, and an enhanced memory for anxiety-provoking situations (8). Taken together, the results of these studies suggest that disturbances in information processing are essential features of depression and anxiety disorders. Similarly, CBT has also been adapted to disturbances in information processing particular to other psychiatric conditions, including eating disorders, substance abuse, personality disturbances, and psychosis (20, 25–32). Specific applications of CBT treatment strategies are described later in the chapter.

35.1.2. Behavioral Model

Learning theory, which dates to the work of Pavlov (33) and Skinner (34), provides the foundation for the behavioral model of therapy. Research on learning in animals has long examined patterns of acquisition and maintenance of behavior, and abnormal or "neurotic" behaviors in animals can be consistently induced by repeated pairings of a noxious stimulus with a neutral one (i.e., classical conditioning) or shaped by controlling reinforcement schedules (i.e., operant conditioning). It was eventually speculated that behavioral approaches could also be applied to the treatment of psychiatric illness. By the late 1950s, a growing dissatisfaction with medical and psychoanalytic models of psychopathological processes and treatment was evident within the field of academic psychology. Critical problems, such as poor diagnostic reliability and the lack of evidence supporting the effectiveness of psychodynamic psychotherapy, were likewise recognized. The modern psychopharmacologic revolution was still in its infancy, and no alternative paradigm had adequate scientific currency. Moreover, the behaviorists emphasized the scientific investigation of learned and measurable behaviors. Operant conditioning, using contingent reinforcement and/or extinction, was found to be useful in modifying behavior in institutionalized, chronically mentally ill patients. Counterconditioning treatment of anxiety disorders, utilizing systematic desensitization, proved to be another effective behavioral intervention. By the late 1970s, behavioral therapy had become the most influential model of treatment outside of the medical setting. More recently, the behavioral model has incorporated cognitive processes and other individual variables that affect learning. These factors, including the individual's past history, their inherent talents, and the adaptability of their response repertoire, lead to inter-individual variability in stimulus-response relationships (8).

35.1.3. Selection of This Modality

Selection of CBT for an individual patient should be based on the appropriateness of this modality for the particular treatment situation. Relevant questions include: Is the patient psychotic? If so, are there specific target behaviors, and have psychopharmacological interventions been optimized? Does the patient suffer from a disorder known to be responsive to CBT? Among patients with potentially treatable disorders, other indicators of response include chronicity, severity, and comorbidity. A general rule is that patients with acute, mild to moderately severe mood and anxiety disorders are the best candidates for treatment with CBT monotherapy (35). Patients with more chronic, severe, or complicated illnesses may be better candidates for combined treatment strategies such as CBT + medications (36). McCullough has developed a variant of CBT for chronic depression that has shown promise when used alone or in combination with antidepressant medication (37).

An outpatient trial of acute phase CBT for depression or anxiety typically ranges from 10 to 20 treatment sessions (10). Deterioration of the patient, or noncompliance with therapy, may warrant early termination of a treatment trial, and for certain chronic conditions such as borderline personality disorder and bipolar disorder, longer courses of therapy may be indicated (20,

25, 38). Jarrett and Kraft (39, 40) have conceptualized treatment across the acute, continuation, and maintenance phases of depression. We will address these phases of treatment later in this chapter. During treatment of major depressive disorder and panic disorder, a majority of patients who ultimately benefit from CBT will show a significant reduction in symptoms within 6 to 8 weeks of starting therapy (41). Those who show a late response to CBT (i.e., between weeks 12 and 16) may be at higher risk for subsequent relapse (42).

35.1.4. Issues of Gender, Race, and Ethnicity

The cognitive and behavioral therapies appear equally effective for men and women, as well as for individuals of different races and ethnicities (43). As with other forms of psychotherapy, a productive CBT working alliance is based on mutual respect for individual differences (44). For certain patients with gender, racial, or ethnically-related issues, it may be useful to select therapists with special skills or experiences (such as therapists who specialize in gay and lesbian issues, or post-traumatic stress syndromes due to rape). It has been recommended that cognitive-behavioral therapists receive special training and supervision in ways to respond to specific issues related to gender, race, and ethnicity (44).

35.1.5. Preparation of the Patient

Patients are encouraged to read relevant written materials that describe the theory and strategies of CBT. For common disorders, such as major depressive disorder and panic disorder, self-help manuals for patients are now available (45–47). In the near future, it is likely that multimedia programs will have an increasingly important role in therapy preparation (48). Regardless of the mode of application, patients beginning CBT need to become socialized to the following: 1) to be active collaborators (with the therapist) in examining and trying out new behaviors; 2) expectation to complete homework; 3) the progress of therapy will be measured regularly, and strategies will be altered if current ones are ineffective; 4) therapy will be focused on symptoms and social functioning, and will generally be time-limited; and 5) the chance of success after treatment termination can be gauged by the patient's incorporation of therapeutic techniques into their daily life.

35.1.6. Phases of Treatment

Most cognitive and behavioral therapies use a three-stage process. The initial phase includes clinical assessment, case formulation, establishing a therapeutic relationship, psychoeducation, socializing the patient to therapy, and introducing treatment procedures. The middle stage involves the sequential application and mastery of cognitive and behavioral treatment strategies. This stage ends when the patient has reached the desired symptomatic outcome. The final phase of therapy is characterized by preparation for termination. Sessions are scheduled more widely apart, in order to test the durability of treatment and to shift the responsibility for using therapeutic strategies from the therapist to the patient. Another goal of this stage is relapse prevention. Strategies to reduce vulnerability to stress or high-risk situations are reviewed, including identification of prodromal symptoms, rehearsal of self-help procedures, and establishment of guidelines for return to treatment (49). The failure to achieve remission of depressive symptoms after 16 to 20 weeks of therapy indicates a need for additional treatment. Incomplete symptomatic remission after 20 weeks of CBT may also indicate the need for adding pharmacotherapy to the treatment regimen.

35.1.7. Intensity and Duration of Treatment

Outpatient CBT is normally conducted once or twice a week. In selected cases, more frequent intervals may be useful, but the cost-effectiveness of such an approach is uncertain. When patients are seen in a day treatment hospital or inpatient setting, sessions are typically provided on a daily or every-other-day basis, and often blend individual and group therapy (29). In our experience, more frequent sessions are needed to overcome demoralization in severely ill patients (50). In most cases, the duration of a CBT course is 3 to 6 months. For those who begin therapy as inpatients, a similar period of aftercare is strongly recommended (49). Unsuccessful therapy (e.g., failure to achieve significant symptomatic improvement) should generally not continue past 12 to 16 weeks for outpatients.

35.1.8. Augmentation of Therapy

It is now common to add an appropriate form of pharmacotherapy to the treatment regimen of depressed patients as they undergo CBT. In some cases, the neurobiological substrate of the illness may be too severe to be responsive to the CBT intervention without concomitant pharmacotherapy (92). In clinical practice, psychiatrists who are trained in CBT often combine cognitive therapy and pharmacotherapy from the beginning of treatment, unless the patient expresses a strong desire to receive psychotherapy alone.

There are no contraindications to combining CBT and pharmacotherapy (11). In fact, these modalities are highly compatible, both in theory and practice (36). As noted earlier, pharmacological stabilization is a prerequisite for CBT in certain Axis I disorders (including psychotic depression, schizophrenia, and bipolar disorder). Combining pharmacotherapy and CBT requires a well-defined division of labor among providers, with open lines of communication and an explicit sense of collaboration (92). Treatment of patients with severe, refractory, or incapacitating mood and anxiety disorders may represent the best use of combined therapies (52). Other strategies that enhance CBT include increasing the frequency of visits, switching emphasis (i.e. from a predominantly cognitive to a more behavioral focus, or vice versa), or involving a spouse or significant other in the therapy. The latter strategy has been shown to be particularly useful in cases of depression associated with marital discord (53, 54). Computer augmentation is a new addition to the tools available to CBT practitioners (48, 55, 56). Greater availability of personal computers with multimedia capability and smart-phone APPs, along with increasing pressure to reduce the cost of treatment, are making such form of therapy augmentation a more common practice in clinical settings. Several groups have published reports examining the use of internet-based CBT in the treatment of conditions such as OCD, panic disorder, and perfectionism (94, 178, 179), and a recent meta-analysis of computerized CBT for depression supported the efficacy of this modality, though also noted that cost-effectiveness remains to be demonstrated (180).

35.1.9. Continuation and Maintenance Phase CBT

Because some patients do not completely achieve remission of symptoms (defined as a return to their premorbid well state) and because many patients experience depression as a recurring illness, there is a notable need for longer-term treatment methods, especially for major depression (57). Incomplete remission of depression leads to recurrence, often resulting in further economic, interpersonal, and medical consequences (58). Failure to achieve complete remission of the index depressive episode by the sixth week of acute phase CBT is associated with a threefold to fivefold increase in subsequent risk of relapse or recurrence. Thase and colleagues (42) have found that between 50–60% of CBT responders meet this criterion for risk, and Jarrett's group has demonstrated that an 8 month course of continuation-CBT (C-CBT) essentially neutralizes this higher risk of relapse (39). C-CBT focuses on the vulnerabilities for recurrent depression in three domains: biologic (genetics, biology, familial, developmental), psychosocial (personality, interpersonal, social), and cognitive (40). By identifying and modifying risks and vulnerabilities, and learning more effective ways to manage mood symptoms, C-CT helps patients prevent relapse and recurrence (181).

Fava (59) has developed another interesting approach to reduce the risk of relapse, which involves the sequencing of treatment depending upon degree of response following acute phase therapy. Fava and colleagues found that a 12 session course of CBT focusing on healthy lifestyle changes significantly reduced depressive symptoms, increased the likelihood of successfully withdrawing from antidepressants (60, 61), and decreased the risk of subsequent relapse after withdrawing antidepressant medications (62). Other studies (63, 64) support the strategy of using a short course of focused CBT to offset the risks of relapse and recurrence of major depression. After more than 1 year of follow-up, Evans and colleagues found that CBT responders had the same rates of relapse as antidepressant responders treated with ongoing pharmacotherapy (93). The risk for relapse after CBT may be particularly low for patients who achieve complete remission before ending treatment (42). The addition of CBT for relapse prevention in medication non-remitters has also been advocated (59).

35.2. Efficacy of CBT

The cognitive and behavioral therapies are, as a class, the best-studied form of psychotherapy. Numerous research studies have demonstrated their efficacy for a variety of Axis I disorders (65).

35.2.1. Mood Disorders

Evidence for the efficacy of Beck's model of CBT for the treatment of mood disorders originates from studies of outpatients with nonpsychotic major depressive disorder (MDD). CBT is an effective treatment for MDD, compared with a waiting list

control condition (35). Since an initial study by Rush and colleagues (66), a major research focus has been to establish the efficacy of CBT vis-á-vis antidepressant pharmacotherapy. Controlled trials contrasting CBT and tricyclic antidepressants have been completed (37), as have a legion of studies using other designs and comparison groups (35, 67). Only a few published trials of CBT have included a placebo plus clinical management condition (68–70). In addition, several meta-analytical reviews have been published (71, 72). Results of these studies indicate that CBT is generally comparable in efficacy to treatment with tricyclic antidepressant medication (65). A retrospective comparison of consecutive cohorts treated with CBT or supportive counseling and pill-placebo suggests that CBT has greater therapeutic effects than this competently administered control condition, which is the ideal comparator for pharmacology efficacy studies (73).

Several large and important studies have compared CBT and medications. The influential National Institute of Mental Health Treatment of Depression Collaborative Research Program (TDCRP) (68), a large, controlled, three-site clinical trial, found that CBT fell between the imipramine plus clinical management condition (i.e., not significantly less effective) and the placebo plus clinical management condition (i.e., not significantly more effective). Furthermore, in more severely ill patients or in patients with greater functional impairment, CBT appeared to be less effective than imipramine and slightly, although not statistically, less effective than interpersonal psychotherapy (another time-limited, depression-focused psychotherapy, which stresses here-and-now, interpersonal issues as the predominant focus of the therapy). When this same cohort was observed over the course of 18 months of follow-up, it was determined that there was no significant difference among any of the treatments with respect to the number of patients who recovered and remained well. However, CBT patients had the lowest rates of receiving some form of treatment during the follow-up period, and had the lowest rates of relapse after 18 months, suggesting perhaps greater durability (74). The acute-phase treatment findings of TDCRP have raised questions about the suitability of CBT as a treatment for severe depression (75). On the other hand, the adequacy of CBT training and validity of the models of CBT provided in the TDCRP trial have been challenged (76, 77). Furthermore, other investigators have found CBT to be as efficacious as pharmacotherapy (70, 78–80). Additionally, CBT has been demonstrated to be effective for inpatients with severe and chronic depression (81).

Additional evidence for the benefit of CBT in severely ill and chronically depressed patients, as well as the added benefit of combining CBT and medication, comes from a large, multi-site, randomized clinical trial using McCullough's CBT-based treatment—The Cognitive-Behavioral Analysis System for Psychotherapy (CBASP) (37, 82). CBASP demonstrated equal efficacy to the serotonin-norepinephrine reuptake inhibitor, nefazodone, and each was effective in 48% of cases. The combination of the two treatments also produced an impressive response rate of 73% at the end of 12 weeks of treatment (intent-to-treat analyses). Thus, efficacy has been demonstrated for a form of CBT that specifically addresses the problems of severe and chronically depressed patients. Additionally, in an interesting study using PET scanning technology, Mayberg and colleagues found different regional metabolic changes in patients treated with paroxetine and CBT. Treatment with CBT was associated with characteristic metabolic changes in the frontal cortical regions of the brain, whereas medication treatment altered metabolism in the brainstem limbic regions (83, 84). The authors suggested that combining these two modalities might synergistically improve treatment outcome. Similarly, in a meta-analysis of randomized controlled trials of combination CBT and medications (including amitriptyline, clomipramine, nortriptyline, desipramine, and nefazodone) versus medications alone, the authors found that the likelihood of response was almost twice as high in the combination group (36). Fournier and colleagues recently described pre-treatment variables associated with response to medications or CBT for moderate to severely depressed outpatients (182). Chronic depression, older age, and lower intelligence each predicted relatively poor response across both treatments, while marriage, unemployment, and greater number of recent life stressors predicted superior response to cognitive therapy relative to antidepressant medications.

The more recent Sequenced Treatment Alternative to Relieve Depression (STAR*D) study, a 41-site, effectiveness study, compared second-step treatments for unipolar (nonpsychotic) depressed patients who failed to achieve remission with an adequate trial of the SSRI citalopram. Subjects in the switch group were randomized to sertraline (an SSRI), bupropion SR (a non-SSRI antidepressant), venlafaxine XR (a dual-acting agent), or CBT. For these treatment-refractory individuals, CBT was as effective as the medications in producing remission of depressive symptoms (85).

Group CBT strategies for treatment of depression have been found to be nearly as effective as individual treatment in both direct comparisons (86) and meta-analytical comparisons (72, 87). These studies suggest that significant savings in cost-effectiveness might be gained by more regular use of group treatments. One study (88) in dysthymic patients compared the efficacy of sertraline and group cognitive behavioral therapy, alone or in combination. The authors found that group CBT was less effective than sertraline in alleviating clinical symptoms. However, CBT augmented the effects of sertraline with respect to some functional changes, and in a subgroup of patients it attenuated functional impairments that are characteristic of dysthymia.

Marital CBT is an effective treatment for depression associated with marital discord (53, 54). When effective, marital therapy also provides improvement in dyadic adjustment, whereas the effects of individual CBT are primarily limited to symptomatic improvement (53, 54). Because marital discord plays a major role in the pathogenesis of many depressive episodes, greater use of couples treatment strategies may be appropriate (89, 90), and such strategies have been described (91).

Other models of cognitive and behavioral therapy have also been studied in randomized clinical trials of major depressive disorder, and they have generally matched or exceeded the results of the antidepressant condition (95–97). In two studies, the combination of behavioral therapy and antidepressants resulted in more rapid improvement (96, 98). Behavioral strategies emphasizing self-control and problem-solving skill, and increasing pleasurable activities, have also been found consistently superior to waiting-list control conditions (35, 72).

35.2.2. Anxiety Disorders

Controlled studies have established the efficacy of CBT for generalized anxiety disorder, obsessive-compulsive disorder, simple phobia, social phobia, panic disorder, and agoraphobia (99–105, 183). CBT has also been shown to be an effective treatment for anxiety disorders in older adults, at the end of therapy and over 12 months of follow-up. This latter study included patients with a wide range of anxiety disorders to allow generalization to a "real-world" population (106).

For simple phobias, CBT emphasizing progressive (graded) exposure, systematic desensitization, relaxation training, and homework assignments are considered to be the first-choice psychotherapeutic treatment (99, 102, 107). Obsessive-compulsive disorder is also amenable to CBT interventions (184), with response rates of 50% to 70% typically reported (108–110). Behavioral strategies of exposure and response prevention are especially useful (108, 109, 111), and have been found to be comparable to anti-obsessional medications such as clomipramine in patients with compulsions (108, 112). Interestingly, in a small study by Baxter and colleagues, behavioral treatment of obsessive-compulsive disorder reduced glucose metabolism in the caudate nucleus (a putative site for obsessive-compulsive disorder) comparable to patients treated with pharmacotherapy (113).

Generalized anxiety disorder and social phobia (185–187) are common conditions, often presenting with depressive and Axis II comorbidity. CBT for anxiety disorders emphasizes relaxation training, cognitive coping skills, social skills training, and graded exposure to feared situations, and has generally been shown to be superior to waiting list or nonspecific therapy control conditions (104, 114–118). An average of 60% to 80% of patients treated in clinical trials have responded to cognitive and behavioral methods (119, 120). In a controlled trial of patients with generalized anxiety disorder comparing CBT to Behavioral Therapy (BT) and a wait-list control group, results showed a clear advantage for CBT over BT. There was a consistent pattern of change favoring CBT in measures of anxiety, depression, and cognition (116). A randomized, controlled trial in older adults with GAD of CBT versus a nondirective supportive psychotherapy found no significant difference between the treatments, although both reduced anxiety and depression (121). A meta-analysis of the extant controlled outcome studies found that CBT for GAD produces significant improvement that is maintained for up to one year following treatment termination (122). A more recent meta-analysis of studies of CBT for anxiety, tested under well-controlled conditions, found that results from effectiveness studies were in the range of those obtained in efficacy trials (188).

The comparative efficacy of cognitive and behavioral treatments and pharmacotherapy for panic disorder and agoraphobia has also been intensively investigated (123, 100, 101, 124, 125, 189, 190). These treatments teach patients to disregard or deemphasize internal cues linked to sensitivity to anxiety, while mastering behavioral self-control strategies such as breathing exercises and deep muscle relaxation. Cognitive strategies are also used in these models to decrease exaggerated thinking patterns (e.g., catastrophic thinking) and reduce worrying.

In general, between 70% and 90% of patients treated with CBT become panic free within 2 to 4 months of beginning therapy (100, 102, 125). The specific models of CBT introduced by Beck and Emery (32), Clark (126), and Barlow and Cerny (127) have been shown to be superior to waiting list or nonspecific control conditions (124, 128, 129). In a study using an across-subjects design, CBT had significant superiority to information-based therapy in reducing panic attacks in patients with panic disorder and secondary depression (130). Meta-analyses (32, 102) suggest comparability of CBT and pharmacotherapy (i.e., tricyclic antidepressants or potent benzodiazepines) during acute phase therapy. In one trial, the selective serotonin reuptake inhibitor fluvoxamine was superior to CBT (131). However, in other studies, similar advantages favored CBT (124, 132, 133).

Even if comparably effective, the cost-efficiency of pharmacological treatment may be reduced (relative to CBT) by high rates of relapse after discontinuation of pharmacotherapy (134–136). Evidence collected to date suggests that there may be fewer relapses after cessation of CBT compared with relapse rates after medication discontinuation (137). This prophylactic effect may be related to significant changes in neurophysiological sensitivity (101). For example, Shear and colleagues (138) found that successful CBT resulted in significant reduction of patient sensitivity to sodium lactate, a biological probe that reliably induces panic attacks in a significant number of patients susceptible to panic.

As with treatment of depression, CBT has shown value when used sequentially to reduce the risk of relapse after withdrawal of pharmacotherapy (137, 139). However, evidence does not indicate that combining CBT with pharmacotherapy yields a strongly synergistic effect (100, 133, 140–142) in the treatment of patients with panic disorder.

There is also interest in the application of CBT to post-traumatic stress disorder. A review of controlled outcome studies indicated that CBT is the psychological treatment of choice, and is more effective than eye movement desensitization and reprocessing (143).

35.2.3. Eating Disorders

The efficacy of CBT for bulimia nervosa has been demonstrated in many research studies (144–152). Reviews of controlled studies have found strong evidence for the efficacy of CBT (153, 154). Combined cognitive and behavioral therapy has been shown to be superior to a behavior monotherapy approach to bulimia (155). At follow-up assessment after six months of treatment, 69% of subjects who received CBT reported no binge eating and purging, as compared to 38% in the behavior therapy group and 15% in the attention placebo group. Reviews of research on combined CBT and pharmacotherapy for bulimia have found that CBT has an additive benefit to antidepressant therapy (153, 154). One recent clinical trial compared two maintenance treatment conditions for weight-restored anorexia nervosa (AN)—individual cognitive behavior therapy (CBT) and treatment as usual (TAU)—and found that time to relapse was significantly longer in the CBT condition when compared with TAU, suggesting that CBT may be helpful in improving outcomes and preventing relapse in weight-restored anorexia nervosa (191). A recent report by Poulsen and colleagues compared psychoanalytic psychotherapy and CBT for treatment of bulimia nervosa, and interestingly found that despite the disparity in the number of treatment sessions and the duration of treatment, CBT was more effective in relieving binging and purging than psychoanalytic psychotherapy and was generally faster in alleviating eating disorder features and general psychopathology (51). There has also been interest in the use of CBT for treatment of obesity, and a recent study examined whether the addition of cognitive therapy to a standard dietetic treatment for obesity might prevent relapse. The cognitive dietetic treatment was found to be significantly better than exercise dietetic treatment in longer-term outcomes, as participants in the CBT/dietetic treatment maintained all of their weight loss, whereas participants in the physical exercise/dietetic treatment regained part (25%) of their lost weight (192).

35.2.4. Bipolar Disorders

Randomized control trials of CBT in patients with bipolar disorder have been conducted, the first of which studied whether CBT improved lithium compliance at 6 and 12 months after treatment, as compared to a control group. The results of this study indicated no difference in lithium compliance on self-reports, informant-reports, or lithium compliance, but unblinded physicians reported increased compliance in the patients who received CBT (156). A second study by Lam and colleagues examined the use of CBT to prevent relapse in bipolar patients who were taking mood stabilizer medications. Modifications to traditional CBT for depression included: 1) a psychoeducational component that modeled bipolar illness as a stress-diathesis illness; 2) teaching CBT skills to cope with symptoms of bipolar disorder that are characteristic of the patient's illness pattern; 3) promoting the importance of circadian regularity by emphasizing the importance of routine and sleep; and 4) dealing with the long-term vulnerabilities and difficulties of the illness. Therapy consisted of 12–20 sessions and lasted 6 months, and outcomes were measured at 6 and 12 months and compared to a treatment as usual group. The CBT group had significantly fewer bipolar episodes, higher social functioning, better coping strategies for bipolar problems, evidence of less fluctuation in symptoms of mania and depression, less hopelessness, better medication compliance, and also used significantly less neurologic medication (157). These benefits persisted after 2 years of naturalistic follow-up (158). Such results support the findings of Scott and colleagues, who have found a benefit for CBT treatment in preventing relapse of bipolar disorder (159). In a small pilot study, lacking a control group, Zaretsky and colleagues suggest that CBT may be a beneficial adjunct to mood stabilizers in depressed bipolar patients (160).

35.2.5. Other Disorders

Dialectical Behavior Therapy (DBT) is an effective treatment for borderline personality disorder. This modified form of CBT incorporates Zen practices of mindfulness and acceptance. DBT teaches patients to control para-suicidal, suicidal and treatment interfering behaviors, in order to improve coping skills and decrease mood lability and interpersonal conflict (25, 161, 162). In a large randomized trial of DBT versus carefully matched expert community therapists, subjects receiving DBT were half as likely to make a suicide attempt, required less hospitalization for suicidal ideation, and had lower medical risk

across all suicide attempts and self-injurious acts combined. The authors concluded that DBT appears to be uniquely effective in reducing suicide attempts (163). Cognitive and behavioral therapies have also been studied in substance abuse disorders, and tend to be more effective than standard counseling approaches alone in patients with concomitant psychiatric illness (164–166). The directive methods employed by cognitive-behavioral therapists may reduce "resistance to change" that is characteristic of substance-abusing patients, who may have limited ability to make use of reflective and insight-oriented strategies (167).

CBT has also been successfully used to treat insomnia. Sivertsen and coworkers performed a randomized, double blind, placebo-controlled study of older adults with chronic insomnia. They compared CBT and pharmacological treatment and found the CBT intervention to be superior to treatment with zopiclone, both acutely and over 6 weeks. CBT techniques included psychoeducation about sleep hygiene, sleep restriction, stimulus control, relaxation techniques and cognitive interventions (168). In a recent paper (193), Mitchell and colleagues systematically reviewed RCTs comparing CBT to medications for patients with insomnia, and found low to moderate grade evidence that CBT is superior to benzodiazepine and non-benzodiazepine drugs in the long term, and very low grade evidence that benzodiazepines are more effective in the short term. Overall, CBT can be effective for treating insomnia, and its effects may be more durable than those of medications.

For the psychotic Axis I disorders, including schizophrenia, the cognitive and behavioral therapies have been shown to be useful adjunctive treatments for patients stabilized with appropriate psychotropic agents. The first uncontrolled trials of CBT for psychosis suggested that CBT could be used effectively to reduce hallucinations, delusions, and other symptoms of schizophrenia (169–172). Subsequently, several randomized controlled trials have found an additive benefit when CBT is combined with medication (173–177). For example, Drury and colleagues (173, 174) observed greater improvement in positive symptoms in hospitalized patients who received CBT, as opposed to those receiving nonspecific and supportive treatment. This group also observed reduced time to recovery in patients treated with CBT. Sensky and colleagues (177) studied ninety treatment-refractory patients with schizophrenia. Both CBT and an equal amount of time of supportive therapy were effective at the end of active treatment. However, nine months after treatment, subjects who received CBT had significantly lower ratings on measures of positive and negative symptoms.

Lincoln and colleagues (194) examined the effectiveness of CBT for psychosis (CBTp) in routine clinical practice settings, by randomizing subjects to CBTp or wait-list control over a 1 year follow up period. The CBTp group showed significant improvement over the wait list group on total Positive and Negative Syndrome Scale score at post-treatment. CBTp was also superior to the wait list group on secondary outcomes of positive symptoms, general psychopathology, depression, and functioning, but not on negative symptoms. Participants also perceived the treatment as helpful and considered themselves improved. A recent Cochrane review of twenty clinical trials examined the effects of CBT for individuals with schizophrenia, compared to other psychological interventions (195). When CBT was compared with other psychosocial therapies, no difference was found for outcomes relevant to adverse events, and time to relapse was not reduced. More specific measures failed to show differential effects on positive or negative symptoms of schizophrenia, but there was some suggestion of longer-term effects of CBT with regards to improving affective symptoms.

35.2.6. Mindfulness-Based Cognitive Therapy

Over the past decade, "Mindfulness-Based Cognitive Therapy" (MBCT) has gained popularity in research and clinic practice. Mindfulness-based treatments "emphasize achieving a mental state characterized by present-moment focus and non-judgmental awareness," with a major aim being to "improve emotional well-being by increasing awareness of how automatic behavioral and cognitive reactions to thoughts, sensations, and emotions can cause emotional distress" (196). MBCT is an extension of traditional CBT, and was initially developed by Segal, Williams, and Teasdale to prevent relapse among patients who had recovered from depression. By focusing on the "present moment," it is proposed that patients with a history of depression are "less likely to fall into the ruminative patterns of negative and hopeless thinking that characterized previous episodes" of depression (196). Although mindfulness-based treatments and traditional CBT are closely related, important differences do exist. Unlike CBT, which focuses on changing the content of thoughts, MBCT teaches patients to adopt a broader "de-centered" perception of their thoughts as "mental events" that do not necessarily reflect self or reality (196). In a recent review, Coelho and colleagues (197) examined evidence from randomized trials of MBCT, and found that for patients with multiple previous depressive episodes, MBCT demonstrated an additive benefit to usual care. A pilot study by Barnhofer and colleagues (198) investigated the effectiveness of MBCT in patients suffering from chronic-recurrent depression, and found that self-reported symptoms of depression decreased from severe to mild in the MBCT group, with no significant change in the treatment as usual group. Similarly, the number of patients meeting full criteria for depression decreased significantly more in the MBCT group.

In addition to its use in the treatment of depression, MBCT has been adapted to treat a broad array of anxiety disorders, including GAD, panic, social anxiety, and hypochondriasis. McManus and colleagues (199) conducted a controlled trial of

mindfulness-based CBT for hypochondriasis, and found that MBCT participants had significantly less health-related anxiety than participants who received "unrestricted services," both immediately following the intervention and at one-year follow-up. The authors suggested that MBCT may be a useful addition to usual services for patients with health-related anxiety. In a small trial, Britton and colleagues examined MBCT as it pertains to emotional reactivity (200), and found that MBCT was associated with decreased emotional reactivity to social stress, while waitlist controls showed an increase in anticipatory anxiety that was absent in the MBCT group. Improvements in emotional reactivity also partially mediated improvements in depressive symptoms.

35.3. Conclusion

The cognitive and behavior therapies are based on well-articulated theories that have strong empirical evidence. These therapies emphasize objective assessments and use of directive interventions aimed at reducing symptomatic distress, enhancing interpersonal skills, and improving functioning. Cognitive interventions are focused primarily on identifying and modifying distorted thoughts and pathological schemas. Behavioral techniques to increase exposure, increase activity, enhance social skills, and improve anxiety management are useful modalities, and can complement or amplify the effects of cognitive strategies. Similarly, the cognitive perspective can add depth to behavioral modalities by teaching patients how to recognize and modify their attitudinal vulnerabilities.

The cognitive and behavioral therapies are the best-studied psychological treatments for major depression, panic disorder, generalized anxiety, and obsessive-compulsive disorder. Overall, there is good evidence for effectiveness within these indications. Cognitive and behavioral therapies have also been adapted for adjunctive use with pharmacotherapy for treatment of bipolar disorder and schizophrenia. Overall, the cognitive and behavioral therapies have become one of the standard psychosocial approaches for the treatment of mental disorders

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36
Forensic Psychiatry

Charles L. Scott, M.D. and Phillip J. Resnick, M.D.

Abstract Forensic psychiatry involves those aspects of psychiatry that interface with the legal system. This chapter addresses the following five areas of forensic psychiatry that a general psychiatrist may likely encounter during their career: (1) assessment of malingering; (2) assessment of dangerousness; (3) competency; (4) criminal responsibility; and (5) expert witness testimony. The important principles described in this chapter will assist mental health professionals in their general practice.

Keywords Malingering · Competency · Insanity · Malpractice · Expert witness · Dangerousness · Forensic psychiatry

36.1. Overview

Forensic psychiatry involves those aspects of psychiatry that interface with the legal system. The American Academy of Psychiatry and the Law provides a more detailed definition of forensic psychiatry in its Ethics Guidelines which states the following: "Forensic Psychiatry is a subspecialty in which scientific and clinical expertise is applied in legal contexts involving civil, criminal, correctional, regulatory matters, and in specialized clinical consultation in areas such as risk assessment or employment" (1).

There are fundamental differences in the roles and responsibilities of a forensic psychiatrist when compared to the practice of other psychiatric subspecialties. First, the forensic psychiatrist is not typically providing treatment to the evaluee. Instead, the forensic psychiatrist is usually retained by a third party to conduct a psychiatric evaluation that addresses a specific question for legal purposes. Second, the information obtained by the forensic psychiatrist is generally not confidential as there is an expectation that the results of the evaluation will be communicated to another party or agency. Third, whereas a treating provider's primary allegiance is to the patient, the forensic psychiatrist's allegiance is to justice, that is providing an honest and objective evaluation that may or may not be ultimately helpful to an outcome desired by the evaluee. For example, a patient who has been involved in a motor vehicle accident and is seeking financial damages may claim that he/she experiences post-traumatic stress disorder symptoms as a result of the incident. A treating psychiatrist may accept the patient's statements at face value and provide treatment. In contrast, a forensic psychiatrist should pursue verification of alleged symptoms from outside sources and collateral informants (2). Despite these important differences, a general psychiatrist will likely conduct a forensic psychiatric evaluation at some point in their career. This chapter addresses the following five areas of forensic psychiatry:

C.L. Scott, M.D. (✉)
Associate Clinical Professor of Psychiatry, Chief, Division of Psychiatry and the Law, Department of Psychiatry and Behavioral Sciences, University of California at Davis, Davis, CA, USA
e-mail: charlesscottmd@gmail.com

P.J. Resnick, M.D.
Professor, Department of Psychiatry, Director, Division of Forensic Psychiatry, Case Western Reserve University School of Medicine, Cleveland, OH, USA
e-mail: phillip.resnick@case.edu

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- Malingering
- Assessment of dangerousness
- Competency
- Criminal responsibility
- Expert witness testimony

36.2. Assessment of Malingering

Malingering is defined as deliberate production of symptoms motivated by a clearly obvious external goal such as avoidance of criminal prosecution, wanting to obtain financial reward, or avoidance of responsibilities. The DSM-5 notes that malingering is not a condition attributable to a psychiatric disorder (3). Clinicians should be particularly attuned to the possibility of malingering in individuals who may be involved in situations with potential for secondary gain, such as lawsuits alleging psychiatric damages or claims of psychiatric disability in a workplace setting.

The frequency of malingering is related to the setting and circumstance of the evaluation. In a general psychiatry setting, malingering of psychiatric symptoms has been strongly suspected or diagnosed in 13% of patients evaluated in an urban emergency room (4) and between 10 and 12% of patients hospitalized for suicidal ideation (5). In forensic evaluations, the base rate of malingering is higher than in a nonforensic context. For example, between 8 and 33% of individuals psychiatrically assessed in personal injury evaluation are considered malingering (6, 7) and over 20% of individuals referred for evaluations of insanity are determined to have definite or suspected malingering (8).

The following clues may be helpful when evaluating malingered psychosis (9).

1. Malingerers may overact their part (10). Malingerers sometimes mistakenly believe that the more bizarrely they behave the more psychotic they will appear.
2. Malingerers are often eager to call attention to their illness, in contrast to schizophrenic patients, who are often reluctant to discuss their symptoms (11).
3. It is more difficult for malingerers to successfully imitate the form, than the content of schizophrenic thinking (12). Common errors include the beliefs that nothing must be remembered correctly, and that the more inconsistent and absurd the discourse, the better the deception. If the imposter is asked to repeat an idea, he may do it quite exactly, whereas the genuine schizophrenic patient will often wander off on a tangent. The psychotic's train of thought is typically abrupt and changes rapidly; the malingerer may show premeditation and hesitation in presenting a succession of ideas (13).
4. Malingerer's symptoms may fit no known diagnostic entity and may have an unusual combination of symptoms from various types of psychoses.
5. Malingerers may claim the sudden onset of a delusion. In reality, systematized delusions usually take several weeks to develop (14).
6. A malingerer's behavior is not likely to conform to his alleged delusions whereas acute schizophrenic behavior usually does in the first few weeks of a psychosis (15).
7. A malingerer may tell a far-fetched story to fit the facts of his crimes into a mental disease model.
8. Malingerers are more likely to have contradictions in their accounts of the crime. The contradictions may be evident within the story itself; they may also be between physical evidence and the story. When the defendant is caught in contradictions, he may either sulk or laugh with embarrassment (16).
9. Malingerers tend to present themselves as blameless within their feigned illness.
10. Malingerers are likely to repeat questions or answer questions slowly, to give themselves more time to make up an answer. There may be frequent replies of, "I don't know."
11. Malingering should be suspected in defendants pleading insanity if a partner was involved in a crime. Most accomplices of normal intelligence will not participate in psychotically motivated crimes.
12. Malingerers are more likely to have nonpsychotic alternative motives for their behavior, such as killing to settle a grievance or avoid apprehension. Genuine psychotic explanations for rape, robbery, or check forging are unusual.
13. It is rare for malingerers to show perseveration. The presence of perseveration suggests actual organic damage, or an extremely well-prepared malingerer.
14. Malingerers may describe the content of their auditory hallucinations in a stilted manner. One malingerer charged with attempted rape stated that the voices said, "Go commit a sex offense."
15. Malingerers are unlikely to show the negative signs of residual schizophrenia, such as impaired relatedness, blunted affect, concreteness, or peculiar thinking.
16. Persons who have true schizophrenia may also malinger auditory hallucinations to escape criminal responsibility. These are the most difficult cases to accurately assess.

When evaluating malingering, the evaluator should begin by asking open-ended questions about the reported symptoms. This initial approach allows the examinee an opportunity to describe symptoms without specific prompts. Such general questions might include the following (17):

- Describe to me any symptoms that you are experiencing.
- Is there anything else you can tell me to help me understand your situation more?
- When did your symptoms first start?
- Have you ever had any of these symptoms before?
- Have you noticed a change in your symptoms over time?
- Is there anything that you have learned that helps decrease (or tends to worsen) your symptoms?

In addition to the clinical interview, the evaluation of malingering often includes a review of collateral data such as interviews with family members, employment records, police reports, and witnesses' statements, as well as hospital and treatment records. Psychological testing may also be an important component of the evaluation. The Structured Interview of Reported Symptoms (SIRS) is the most validated test for malingered psychiatric symptoms, particularly malingered psychosis (18, 19).

36.3. Assessment of Dangerousness

Dangerousness is not a psychiatric diagnosis like schizophrenia. It is a legal judgment based on social policy. Dangerousness assessments are required in a wide variety of situations that include involuntary commitments, emergency psychiatric evaluations, seclusion and restraint decisions, inpatient care discharges, probation/parole decisions, death penalty evaluations, domestic violence interventions, fitness for duty evaluations, sexually violent predator commitments, and threat assessments.

The accuracy of a clinician's assessment of future violence is related to many factors, including the circumstances of the evaluation and the length of time over which violence is predicted. In 1981, Monahan reviewed clinicians' accuracy at predicting violent behavior toward others and concluded that psychiatrists and psychologists were accurate in no more than one out of three predictions of violent behavior among mentally ill institutionalized patients (20). Fortunately, more recent studies indicate that clinicians' accuracy in assessing future violence has improved particularly when the prediction is limited to assessing risk in male patients over briefer periods of time (21).

When conducting a violence risk assessment, the clinician may find it helpful to divide the concept of dangerousness into five components: (1) the magnitude of potential harm; (2) the likelihood that harm will occur; (3) the imminence of harm; (4) the frequency of dangerous behavior; and (5) situational variables that either promote or protect against aggressive behavior.

The clinical assessment of dangerousness requires a review of several risk factors that have been associated with an increased likelihood of future violence. These factors include an age range in the late teens and early 20s (22), lower socioeconomic status (23, 24), and lower intelligence and mild mental retardation (25). Although males show much higher rates of violent offense than females in the general population, among people with mental disorders (26), men and women do not significantly differ in their base rates of violent behavior (21, 27).

A history of violence is the single best predictor of future violent behavior (28). It is helpful to ask individuals about the most violent things that they have ever done. Obtaining a detailed violence history involves determining the type of violent behavior, why violence occurred, who was involved, the presence of intoxication, and the degree of injury. Criminal and court records are particularly useful in evaluating the person's history of violence and illegal behavior.

A person who has used weapons against others in the past may pose a serious risk of future violence. Subjects should be asked whether they own or have ever owned a weapon. The recent movement of a weapon, such as transferring a gun from a closet to a nightstand, is particularly ominous in a paranoid person. The greater the psychotic fear, the more likely the paranoid person is to kill someone he misperceives as a persecutor.

Drugs and alcohol are strongly associated with violent behavior (29, 30). The majority of persons involved in violent crimes are under the influence of alcohol or drugs at the time of their aggression (31). Stimulants, such as cocaine, crack, amphetamines, and PCP are of special concern.

Studies examining whether individuals with mental illness are more violent than the nonmentally ill have yielded mixed results (22, 32–34). In a study of civilly committed psychiatric patients released into the community, most mentally ill individuals were not violent (35). Although a weak relationship between mental illness and violence was noted, violent conduct was greater only during periods in which the person was experiencing acute psychiatric symptoms. Subsequent research suggests that individuals with schizophrenia may have increased rates of violence even when not experiencing active signs of their illness (36).

The presence of psychosis is of particular concern when evaluating a person's risk of future violence. Douglas et al. (37) found that psychosis was the most important predictor of violent behavior in an analysis of 204 studies examining the relation-

ship between psychopathology and aggression. In paranoid psychotic patients, violence is often well planned and in line with their false beliefs. The violence is usually directed at a specific person who is perceived as a persecutor. Relatives or friends are often the targets of the paranoid individual. In their study of 124 patients with a psychotic diagnosis, Nederlof et al. (38) found that individuals who delusionally believe they are being threatened are more likely to act aggressively when compared with individuals not experiencing such delusions.

A careful inquiry about hallucinations is required to determine whether their presence increases the person's risk to commit a violent act.

Aspects relevant to increased compliance to violent command hallucinations include a belief that the voice is powerful, a person's sense of personal superiority, a belief that command hallucinations benefit the patient, delusions that are congruent with the action described, and hallucinations that generate negative emotions such as anger, anxiety, and sadness (39).

Depression may result in violent behavior under certain circumstances. Individuals who are depressed may strike out against others in despair. After committing a violent act, the depressed person may attempt suicide. Depression is the most common diagnosis in murder–suicides (40, 41). Patients with mania show a high percentage of assaultive or threatening behavior, but serious violence itself is rare (42). Although mania alone does not cause an increase in violence, manic persons who abuse substances are twice as likely to be violent than the general population (43). Patients with mania most commonly exhibit violent behavior when they are restrained or have limits set on their behavior (44).

Brain injury or illness can also result in aggressive behavior. After a brain injury, formerly normal individuals may become verbally and physically aggressive (45). Characteristic features of aggression resulting from a brain injury include reactive behavior triggered by trivial stimuli, lack of planning or reflection, nonpurposeful action with no clear aims or goals, explosive outbursts without a gradual build up, episodic pattern with long periods of relative calm, and a feeling of concern and remorse following the episode.

The most common personality disorder associated with violence is antisocial personality disorder (APD) (28). The violence by those with antisocial personality disorder is often motivated by revenge or occurs during a period of heavy drinking. Violence among these persons is frequently cold and calculated and lacks emotionality (46). Personality traits associated with violence include impulsivity (23), low frustration tolerance, inability to tolerate criticism, repetitive antisocial behavior, reckless driving, a sense of entitlement, and superficiality. The violence associated with these personality traits usually has a paroxysmal, episodic quality. When interviewed, these people often have poor insight into their behavior and frequently blame others for their difficulties (47).

When conducting an assessment of current dangerousness, pay close attention to the individual's affect. Individuals who are angry and lack empathy for others are at increased risk for violent behavior (48). The clinician should also observe the patient for physical signs and symptoms of changes indicating incipient violence. Berg, Bell, and Tupin (49) noted that signs of imminent violence include chanting, a clenched jaw, flared nostrils, flushed face, darting eyes, close proximity to the clinician, and clenched or gripping hands.

In addition to DSM-5 personality disorders or traits, the clinician should also be familiar with the psychological construct known as psychopathy. The term psychopath was described by Cleckley (50) as an individual who is superficially charming, lacks empathy, lacks close relationships, is impulsive, and is concerned primarily with self-gratification. Hare and colleagues developed the Psychopathy Checklist-Revised (PCL-R) (51) as a validated measure of psychopathy in adults. The concept of psychopathy is important because the presence of psychopathy is a strong predictor of criminal behavior and violence among adults (52).

Standardized risk assessment instruments for the prediction of violence are increasingly being used by clinicians in conjunction with their clinical violence risk assessments and include the Hare Psychopathy Checklist-Revised (PCL-R) (51), the Violence Risk Appraisal Guide (VRAG) (53), and the HCR-20 (54). When conducting assessments of dangerousness, mental health clinicians must be careful to balance the protection of society against the patient's loss of freedom. Although decisions about long-term dangerousness are extremely complex, they must be made. Psychiatrists must approach this task with humility and share the decision-making with others concerned with the safety of society.

36.4. Competency

The degree of mental capacity required for competency varies according to the particular task in question. A person who is totally unable to care for himself may require a guardian of person; on the other hand, it is possible to be only incompetent with respect to a specific act, such as entering into a contract. The general criteria for competency are an understanding of the nature of the specific act, and an awareness of the duties and obligations entailed. Since adults are presumed by law to be competent, the burden of proof is on those who think otherwise. Proof of mental incompetence, for any purpose requires the following evidence:

1. The person has a mental disease.
2. The disease causes a defect in judgment.
3. The defect in judgment causes a specific incapacity with reference to the matter in question.

A person who is so impaired that he is unable to take proper care of himself may be declared incompetent. A court-appointed guardian of person is then authorized to manage the incompetent person's finances and care. The guardian of person has the authority to give consent for surgery and placement in a hospital or nursing home. Physicians should always obtain written consent from the guardian before performing medical procedures on an incompetent person.

A guardian of estate, or conservator, may be appointed when a person's incapacity is limited to financial management. For example, impaired judgment, due to mental illness, may cause a person to be: (1) a spendthrift; (2) unwilling to spend money, even for necessities; or (3) unable to protect himself from those who might attempt to secure his property without adequate recompense.

Guardians of estate may advance patients small sums of money for personal purchases. Guardians are answerable to the Court for judicious use of the incompetent ward's funds.

Competency to give informed consent for medical or surgical procedures entails the capacity to understand:

1. The nature of the proposed treatment or procedure.
2. The risks and benefits of the proposed treatment.
3. The likely result if the procedure is not performed.
4. The alternative treatment approaches to the problem.

If a patient has not been adjudicated incompetent, but does not appear capable of giving consent, it is safest to delay elective surgery until guardianship has been obtained.

Testamentary capacity or competency to make a will requires that the person understands that he is making a will and that he knows, without prompting, his natural heirs and the nature and extent of his property. Entering into a contract requires a greater degree of competence than making a will; more judgment is necessitated by the involvement of an adversary interest. In particular, the individual is not only required to understand their personal financial resources necessary to honor the terms of the contract but also the negative consequences for failing to do so. Such negative consequences may include forfeiting financial or personal property and becoming a defendant in civil litigation. A contract is not valid if one of the parties did not have a true understanding of its terms. This lack of understanding must be due to mental disease, not simply a lack of sophistication or technical knowledge.

Competency to marry requires that each partner understands a marriage is taking place as well as the implications of marriage. Competency to be a witness in a court proceeding requires the ability to recall events and understand what it means to tell the truth and take an oath. In the United States, all persons are presumed to be competent to testify.

Competency to stand trial requires that the defendant have a factual and rational understanding of the charges against them and have the ability to assist their attorney in their defense (55). To evaluate the defendant's factual understanding of his/her charges, the examiner typically asks the defendant to explain the charges they are facing, the seriousness and potential legal consequences of being convicted of the charges, roles of various courtroom personnel (i.e., defense attorney, district attorney, judge, jury, witnesses, etc.), possible pleas, and the plea bargaining process. When assessing the defendant's rational understanding of the charges, the evaluator determines the relationship, if any, of mental health symptoms to his/her understanding of the legal situation. For example, if a defendant with paranoid schizophrenia delusionally believes the judge is sending secret brainwave messages instructing the jury to convict, then it is unlikely that this defendant would have a rational understanding of the legal process, regardless if she/he had a factual understanding of the role of the judge and jury.

The examiner also evaluates the defendant's ability to assist his attorney by examining whether or not a mental illness interferes with the defendant's capacity to work with legal counsel. A defendant's refusal to speak to their attorney due to paranoid delusions that the defense attorney is poisoning him/her is evidence that the psychosis renders the defendant unable to rationally assist his attorney. In contrast, a defendant who refuses to speak to his attorney solely because he/she prefers staying in a forensic hospital rather than face potential prison is an unwilling defendant rather than one unable to assist counsel.

A defendant may decide to represent himself or herself without assistance of counsel. The U.S. Supreme Court has held that a nonmentally ill person has a right to self-representation (56). However, the U.S. Supreme Court has also held that a court may deny a mentally ill defendant the right to self-representation, even if the defendant is otherwise competent to stand trial (57). At the time of this writing, no national legal standard has yet been established for evaluating competence to represent oneself.

36.5. Criminal Responsibility (Insanity)

Criminal law is primarily based on blameworthiness. Persons are usually only held criminally accountable for forbidden acts (*actus reus*) done with an evil intent (*mens rea*). If a person commits a crime because of a mental disease or defect that precludes moral blame, he may be found not guilty by reason of insanity. However the mere fact that psychosis or some other type of psychiatric symptom was present when the crime was committed does not assure an insanity finding.

Tests for insanity vary according to the jurisdiction. The McNaughten test requires that mental disease prevented the accused person from either knowing the nature and quality of his act, or that it was wrong (58). This is the most common test of insanity and is used in approximately 38 states (59). This test, sometimes referred to as the "right or wrong test" has been criticized because it is limited to the defendant's awareness of his acts as compared to his ability to control his behavior due to mental illness.

The irresistible impulse test relieves a person of criminal accountability if mental disease made him incapable of refraining from the criminal act. One test of inability to refrain is whether the defendant would have committed the act even if a policeman had been standing at his elbow. The inability to control the impulse must be due to mental illness, not merely a loss of temper or outburst of rage.

The Model Penal Code test, proposed by the American Law Institute (ALI) states, "A person is not responsible for his criminal conduct if at the time of such conduct as a result of mental disease or defect he lacks substantial capacity to appreciate the criminality of his conduct or to conform his conduct to the requirements of the law" (60). At one point, the ALI test was used in 12 of 13 Federal Circuits. However, following John Hinkley's acquittal by reason of insanity for his attempted assassination of President Ronald Reagan, a public outcry resulted in a change in the Federal standard to eliminate the volitional arm of the test as this was perceived as making it easier to be found insane. In 1984, congress passed the Insanity Defense Reform Act which states, "It is an affirmative defense to a prosecution under any Federal statute that, at the time of the commission of the acts constituting the offense, the defendant, as a result of a severe mental disease or defect, was unable to appreciate the nature and quality or the wrongfulness of his acts" (61). The Federal version is now very similar to the original McNaughten test.

Each jurisdiction, either through statute or case law, may provide guidance on which mental illnesses qualify for an insanity defense. Voluntary intoxication with alcohol or drugs is not ordinarily considered a valid basis for an insanity defense. There are however, four specific situations in which intoxication may warrant an insanity defense:

1. Involuntary intoxication.
2. Delirium tremens.
3. Idiosyncratic alcohol intoxication (pathologic intoxication).
4. Permanent psychosis due to alcohol or drug use.

In assessing sanity, the forensic evaluator typically reviews extensive collateral information such as the police reports, witness statements, and autopsy reports in addition to obtaining a detailed account of the crime from the defendant. Factors to be considered when forming a sanity opinion include evidence of mental illness, motive for the crime, degree of planning and preparation for the crime, a detailed understanding of the defendant's thinking and behavior before, during, and after the crime, and the defendant's prior legal and mental health history. Evidence that the defendant had knowledge of wrongfulness may include efforts to avoid detection, disposing of evidence, efforts to avoid apprehension, a statement by the defendant that he knew the act was wrong at the time of the offense, notifying the police that a crime was committed, and expression of remorse or guilt immediately after the crime. In some jurisdictions, the defendant's ability to understand that their actions were morally wrong may also be considered in determining sanity in addition to their knowledge that their acts were against the law. For example, if a person delusionally believes that their neighbor is poisoning members of the community in conjunction with the local police, they may believe that killing this neighbor is morally justified to save others though they hide their actions from the police whom they believe are evil coconspirators.

36.6. Medical Malpractice

Knowledge of general legal concepts assists the clinician in both the provision of mental health treatment and in the understanding of medical legal disputes that may arise during the course of mental health treatment. Tort law governs the legal resolution of complaints regarding medical treatment. A tort is a civil wrong. Tort law seeks to financially compensate individuals who have been injured or who have suffered losses due to the conduct of others.

Negligent torts occur when a clinician's behavior unintentionally causes an unreasonable risk of harm to another. This type of tort is typically used in a malpractice lawsuit against a clinician in a malpractice suit. Medical malpractice is based on the theory of negligence. The four elements required to establish medical negligence are commonly known as the "four Ds." These include a *Dereliction* of *Duty* that *Directly* results in *Damages*. A duty is most commonly established for a clinician when the patient seeks treatment and treatment is provided. The provision of services do not require the patient's presence and can even extend to assessment and treatment provided over the telephone. Dereliction of duty is usually the most difficult component of negligence for the plaintiff to establish. Dereliction of duty is divided into acts of commission (providing substandard care) and acts of omission (failure to provide care). Acceptable care does not have to be perfect care, rather it is that provided by a reasonable practitioner. This standard requires that the provider exercise, in both diagnosis and treatment, "that reasonable degree of care which a reasonably prudent person or professional should exercise in same or similar circumstances" (62).

A psychiatrist is less likely to face a malpractice claim when compared to other medical specialties. For example, the annual probability of a neurosurgeon facing a malpractice claim is 19.1%. In contrast, a psychiatrist has only a 2.6% probability of being sued in any 1 year. However, even though psychiatry is considered a low-risk specialty on an annual basis, an estimated 75% of psychiatrists will face a malpractice claim by the age of 65 years (63).

Common malpractice claims include allegations of incorrect treatment, suicide or attempted suicide, an adverse drug reaction, incorrect diagnosis, and improper supervision of other individuals responsible for providing care to the patient. In a review of psychiatric claims in all 50 states between 1998 and 2009, suicide and attempted suicide was the most frequently identifiable cause of action (64). The possibility of a patient committing suicide represents one of the greatest emotional and legal concerns of clinicians. This concern is realistic in view of the fact that 10–15% of patients with major psychiatric disorders will die by suicide (65). Lawsuits involving suicide usually involve one of three scenarios: (1) an inpatient suicide where the facility and its practitioners provide inadequate care or supervision; (2) a recently discharged patient who commits suicide; or (3) an outpatient who commits suicide (66).

Suicidality is the most common reason for inpatient psychiatric hospitalization (67). When a patient is admitted to the hospital due to thoughts of self-harm, the clinician is on notice that the patient is at an increased risk for suicidal behavior. Nearly one-third of inpatient suicides result in a lawsuit (68). Malpractice actions often name the hospital in addition to the treating clinicians. For example, when hospital staff members are aware of the patient's suicidal tendencies, then the hospital staff assumes the duty to take reasonable steps to prevent the patient from inflicting self-harm (69).

36.7. The Psychiatrist as Expert Witness

Medical reports or testimony are required in over 50% of all trials. The initial reaction to a request for psychiatric testimony may be anxiety or even panic. Psychiatrists are accustomed to assuming positions of authority in hospitals and their own offices. Anxiety may be provoked by the realization that this authority will be challenged by cross-examiners.

Psychiatrists are usually called upon as *expert*, rather than *fact*, witnesses. "Expert witnesses" are persons who possess facts directly related to some science or profession which is beyond the average layperson's scope of knowledge. Only expert witnesses are permitted to offer opinions. A treating psychiatrist may, however, be compelled to testify as a fact witness. A "fact witness" only states his direct observations, such as the information learned during an examination.

It is a fallacy to consider the psychiatric expert witness impartial. Once he has formed an opinion, it is only human for the psychiatrist to identify himself with that opinion, and hope for the success of the side which supports his conclusions.

Psychiatrists sometimes forget that their conclusions are only *opinions.* Juries are instructed that they are to determine how much weight to give the testimony of each witness. A jury has the right to disregard psychiatric testimony, even when it is uncontradicted.

Before beginning a psychiatric evaluation for legal purposes, the psychiatrist has an absolute obligation to explain the absence of confidentiality. Patient-psychiatrist confidentiality may or may not be respected in the courtroom. When asked to reveal personal information about a patient in court, a psychiatrist may suggest to the judge that it should remain confidential. The judge, however, is the final decision maker.

Courtroom procedure is quite formal and ritualized. *Direct* examination will begin with the elicitation of the psychiatrist's qualifications. The psychiatrist will then be asked to describe his examination of the patient. He will be asked whether he has formed an opinion with reasonable medical certainty regarding the legal issue. The term "reasonable medical certainty" simply means that there is a 51% or greater probability that a conclusion is correct, in most states.

The purpose of *cross-examination* is to discredit damaging testimony by demonstrating that the witness is a fool, liar, or nitwit. The psychiatrist's credentials may be attacked by showing a lack of experience or education. Questions may reveal that he has either not completed his board examinations or did not pass them at the first sitting.

The cross-examiner may attempt to show witness bias or personal interest. The adequacy of the psychiatric examination may be attacked because of its length, the absence of privacy, or the lack of corroborating information. The defendant's version of the events in question conflicts with other factual accounts approximately 40% of the time. Consequently, psychiatrists should never base their conclusions entirely upon the evaluee's statements. Psychiatric diagnoses are also highly vulnerable to attack. For example, the DSM-5 field trials examined the test-retest reliability of numerous DSM-5 diagnoses. Field trial results indicated that diagnostic agreement between independent raters ranged from questionable to very good depending on the diagnosis (70).

The following suggestions should enhance the effectiveness of psychiatric expert witnesses:

1. Have a pretrial conference. At this time, the inexperienced witness may be told what to expect.
2. Give your curriculum vitae to the attorney in advance. This will allow him to elicit your qualifications most effectively.
3. Know the specific legal issue and standard. Ask the attorney to enclose these in a cover letter to you, along with the background information.

4. Dress conservatively. A suit conveys more credibility than a loud sports jacket.
5. Leave the courtroom immediately after your testimony.
6. Attempt to display dignity, confidence, and humility.
7. Give short, clear answers in simple language. The boredom factor can cause you to lose the jury's attention.
8. Qualify your answer when necessary. If an attorney demands a "yes" or "no" answer, you may ask the judge for the opportunity to explain your answer.
9. Look at the jury and direct your remarks to them.
10. Do not be, or even appear to be, an advocate. It is your absolute obligation to tell only the truth on the witness stand, regardless of its effect upon the outcome of the case.
11. Do not ever talk down to the jury. If they feel patronized, they will not accept what you are saying.
12. Do not use psychiatric jargon. It is likely to be misunderstood or made to look ridiculous.
13. Do not appear arrogant. Nothing alienates a jury more quickly.
14. Do not attempt to be humorous. A trial is a serious matter.
15. Do not be a smart aleck or argue with the cross-examiner. The jury will ordinarily identify with the witness. If the witness gets smart, however, the jury will take the part of the cross-examiner, in the belief that he is just doing his job.
16. Do not lose your temper.
17. Do not answer any question you do not fully understand. Ask the attorney to rephrase the question.
18. Do not guess at an answer. It is better to say you do not know or do not remember.
19. Do not ever refuse to admit the obvious. It makes the psychiatrist look either foolish or biased.
20. Do not let a zealous attorney push you into an opinion that is not your own.
21. Do not try to avoid answering questions about your fee or pre-trial conferences.
22. Do not be cowed by the judicial process; remember, you are the expert.

The area of law and psychiatry is in a state of flux. Each year, new court decisions further define patients' rights and regulate psychiatric practice. It is, therefore, necessary for each practicing psychiatrist to keep abreast of the laws in his own state.

36.8. Summary

Forensic psychiatry is a broad psychiatric subspecialty that overlaps with the provision of mental health care in many arenas. Important areas of forensic psychiatry reviewed in this chapter include the assessment of malingering, potential dangerousness, competency, criminal responsibility, malpractice, and expert witness testimony. In addition, the underlying legal foundation of forensic psychiatry provides important principles for mental health professionals in their general practice. Such principles include basing assessment and treatment recommendations on evidence-based medicine, continuously striving for honesty and objectivity when conducting evaluations and providing care, understanding the ethical and legal duties to provide safe and effective treatment, maintaining an up to date knowledge base in order to continuously practice within the standard of care, and respecting the dignity and autonomy of those patients we serve.

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37
Sleep Disorders

Thomas D. Hurwitz, M.D., Carlos H. Schenck, M.D., and Imran S. Khawaja, MBBS, FAASM

Abstract Disturbances of sleep are commonly seen in many of the DSM-5 psychiatric disorders. Furthermore, psychiatric symptoms are commonly experienced in association with sleep disorders. This chapter reviews some basic physiology of sleep-wake regulation as well as the most common sleep disorders of importance to the practicing psychiatrist. Included are insomnia, restless legs syndrome, obstructive sleep apnea, narcolepsy, idiopathic and other hypersomnias, and parasomnias such as sleep-walking/sleep terrors and REM sleep behavior disorder. In each case, diagnostic criteria are described, based both upon the American Psychiatric Association Diagnostic and Statistical Manual, Fifth Edition, and the International Classification of Sleep Disorders, Second Edition (ICSD-2). Discussions of epidemiology, clinical features, typical case examples, laboratory findings, course, differential diagnosis, etiology, and treatment considerations will enable the reader to recognize these disorders in their patients and to facilitate their treatment.

Keywords Sleep • Insomnia • Restless legs syndrome • Obstructive sleep apnea • Hypersomnia • Narcolepsy • Parasomnias • Sleepwalking • REM-sleep behavior disorder

37.1. Introduction

Terrestrial life has evolved in an environment of alternating periods of light and darkness. All mammalian species have developed corresponding alternations of rest and activity periods synchronous with the light-dark cycle. During periods of rest, basic changes in physiological and behavioral state are recognized as essential to maintenance of health and survival. By virtue of its importance for preservation of subsequently sustained wakeful attention, it enables vigilance, nutrition, reproduction, and protection against external threats. Furthermore, advances in recent years have demonstrated the importance of sleep for maintenance of metabolic functions including normal glucose homeostasis and preserving the integrity of vascular and other tissues.

T.D. Hurwitz, M.D. (✉)
Assistant Professor, Department of Psychiatry, University of Minnesota School of Medicine, Minneapolis, MN, USA
Department of Psychiatry, Minneapolis VA Medical Center, Minneapolis, MN, USA
Minnesota Regional Sleep Disorders Center, Hennepin County Medical Center, Minneapolis, MN, USA
e-mail: hurwi001@umn.edu

C.H. Schenck, M.D.
Professor, Department of Psychiatry, University of Minnesota School of Medicine, Minneapolis, MN, USA
Department of Psychiatry, Minnesota Regional Sleep Disorders Center, Hennepin County Medical Center, Minneapolis, MN, USA
e-mail: schen010@umn.edu

I.S. Khawaja, MBBS, FAASM
Minnesota Regional Sleep Disorders Center, Hennepin County Medical Center, Minneapolis, MN, USA
Department of Neurology, University of Minnesota, Minneapolis, MN, USA
e-mail: khimran@yahoo.com

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Sleep and its disturbances are important factors influencing the predisposition, precipitation, perpetuation, and manifestations of psychiatric disorders. An inspection of the American Psychiatric Association Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), reveals the presence of sleep symptoms as diagnostic criteria in major depressive disorder, manic and hypomanic episodes, bipolar disorders, persistent depressive disorder, posttraumatic stress disorder (PTSD), acute stress disorder, and generalized anxiety disorder. Indeed, the nightmares of PTSD have been granted "hallmark" significance (2). Additionally, panic disorder may emerge from the sleeping state, dissociative disorders may mimic sleep terrors, and sleep is often perturbed in disorders of substance abuse, dependence, and withdrawal. Disturbed sleep appears to be predictive of subsequent development or relapse of alcohol dependence and depression. Persisting short time latencies between sleep onset and the first REM period, as well as diminished low frequency sleep-EEG activity, have been demonstrated to predict recurrence of major depression (3, 4). This mood disorder is commonly comorbid in patients with insomnia, which may increase the risk of suicide and decrease responsiveness to cognitive-behavior therapy. Furthermore, insomnia may precipitate or worsen manic episodes in bipolar disorder (5–7).

Cognition and learning have been clearly demonstrated to benefit from sleep. Specifically, it appears that the consolidation of some forms of procedural learning and declarative memory are facilitated by sleep. Certainly, the maintenance of sustained attention during wakefulness is directly related to adequate prior nocturnal sleep (8, 9). In view of its effects upon human consciousness, sleep is clearly "of the brain, by the brain, and for the brain" (10).

Physiological manifestations of sleep are measured clinically by polysomnography (PSG), with monitoring of brain electrical activity (electroencephalogram, EEG), eye movements (electrooculogram, EOG), and peripheral muscle tone (electromyography, EMG). These three parameters (supplemented with additional channels when applied clinically) permit distinctions between states of wakefulness and sleep. Since the discovery of Rapid Eye Movement (REM) sleep by Kleitman, Aserinsky, and Dement at the University of Chicago in 1953, these measurements have also characterized the difference between that distinct physiological state and the other stages of (non-REM) sleep. Since 1968, these have been defined by established conventions used to score each 30-second period, or epoch, of a recording (11). These stages have been revised with evidence-based scoring rules published in 2007 and updated as version 2.0 in 2012 (12). The transition from wakefulness to sleep is marked by a shift of EEG rhythm to a relatively low voltage, mixed but slower than wakeful frequency activity typically accompanied by some slow, rolling eye movements, characterizing a transitional stage of non-REM sleep, designated N1. Soon thereafter, the EEG includes intermittent bursts of 12–14 Hz activity known as sleep spindles representing thalamo-cortical interaction associated with decreases of cortical response to peripheral stimuli. Spindles and occasional biphasic waves of 0.5 second duration known as K-complexes define non-REM stage N2 sleep which progresses variably to a pattern of slower, 2 Hz EEG activity that designates stage N3 ($\geq$20% of the 30 second epoch). Prior to the revision of scoring rules, this was divided into stages 3 and 4 defined by slow EEG wave activity occupying >20% or >50% of the 30 second periods, respectively. Absent any distinguishing implications, these former stages are now consolidated as stage N3, often referred to as slow-wave sleep. Because such slower EEG frequencies reflect more synchronous cortical neuronal synaptic activity, these non-REM sleep stages have been called synchronized sleep as distinguished from the low voltage, faster frequency, desynchronized, activity of wakefulness. After about 90 minutes of non-REM sleep, there is typically a period of marked reduction of peripheral muscle tone on EMG, lower voltage (desynchronized) EEG, and intermittent bursts of rapid eye movements defining the stage of REM sleep. This stage also represents a distinct physiological and behavioral state by virtue of continuous muscle atonia (except for occasional fasciculations or twitches), increased cerebral glucose metabolism, genital arousal, variations in cardio-respiratory rhythms, and vivid dreaming. After a variable period of minutes, there is resumption of non-REM sleep before the next periods of REM that recur with a periodicity of around 90 minutes. Each successive REM period is longer in duration with a tendency for more frequent eye movements (Figs. 37.1, 37.2, and 37.3).

37.2. Basic Sleep-Wake Regulation

The regulation of sleep-wake transitions is complex and reflected throughout the neuraxis. As a result of his studies of viral encephalitis lethargica, known in the early twentieth century as "sleeping sickness", Baron Constantin von Economo stimulated the understanding of brain regions mediating this regulation and, by extension, dysregulation. Lesions at the junction of the brainstem and forebrain were associated with periods of prolonged sleepiness, while lesions of the anterior hypothalamus caused prolonged insomnia (13). By mid-century, Moruzzi and Magoun described the reticular activating system from the rostral pons through the midbrain reticular system (14). Interruption of this ascending influence was the cause of the hypersomnia observed by von Economo. Toward late-century, two basic inputs to this arousal system were characterized. One is a pathway from cholinergic cells of the pedunculopontine (PPT) and laterodorsal tegmental (LDT) nuclei of the pons that project to thalamic relay nuclei and the reticular nucleus of the thalamus which is involved in gating of information flow to the cortex. These pontine cholinergic cell groups fire actively during wakefulness as well as REM, but not during non-REM sleep. A second

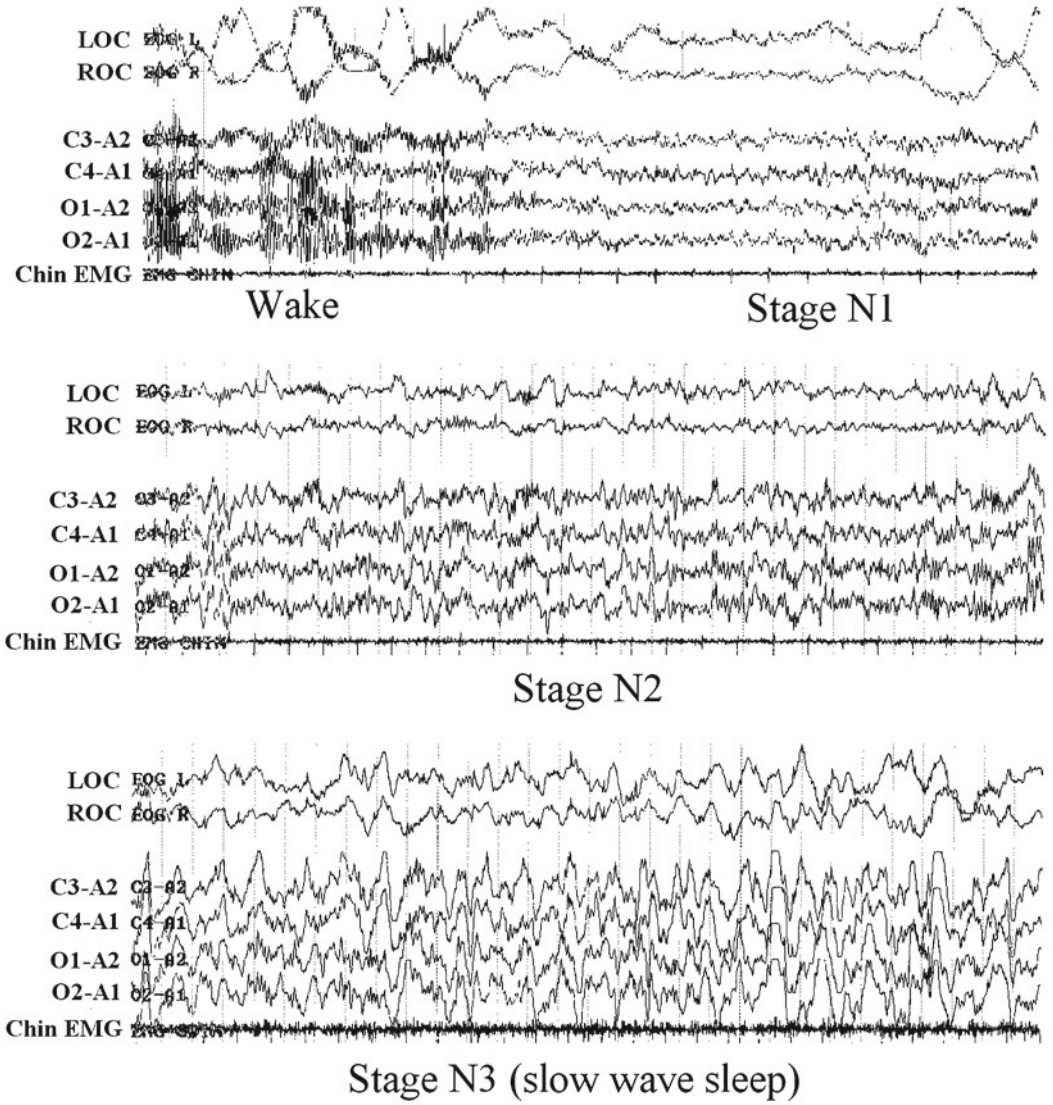
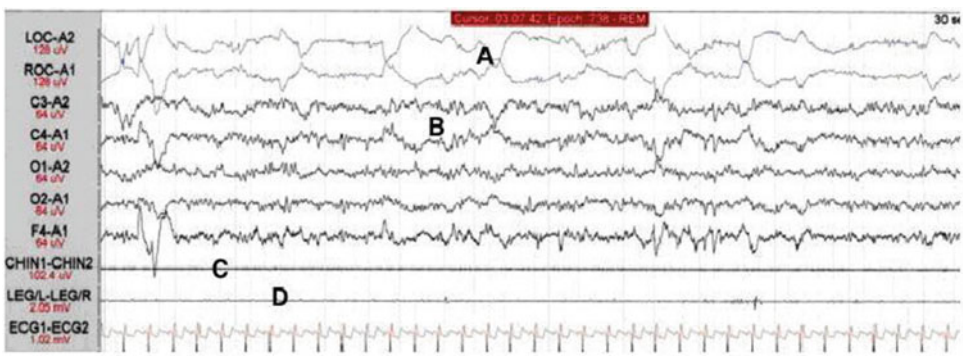


FIGURE 37.1 EEG patterns characteristic of sleep stages. Note the histogram showing the distribution of these patterns over the course of a night, with slow-wave sleep, stage N3 predominantly during the first part of the night. Subsequent non-REM sleep is predominantly stage N2, marked by spindle activity and biphasic K-complexes. Successive periods of REM sleep (when EEG pattern is relatively low voltage and of mixed frequency) become longer as the night progresses.

FIGURE 37.2 A 30-second epoch of REM sleep is exemplified by rapid eye movements (REM's) (A), desynchronized low voltage mixed frequency EEG with occasional saw-tooth wave forms (B), absent muscle tone in the chin EMG (C), and no movement of lower extremities (D).



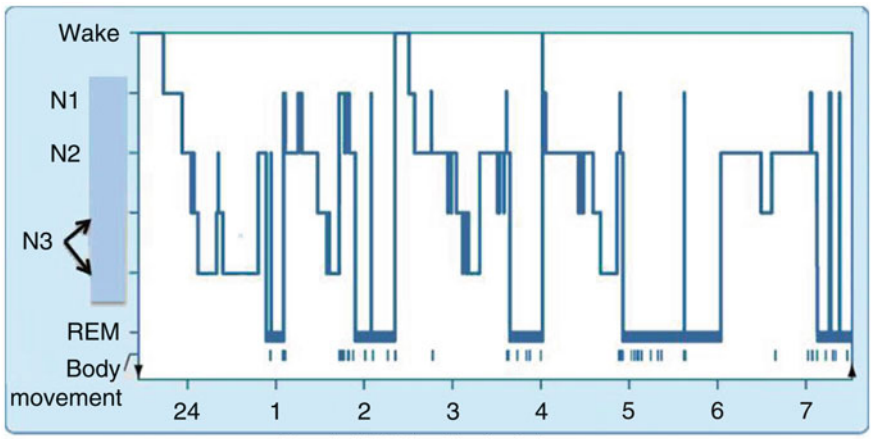


FIGURE 37.3 This histogram shows the distribution of polysomnographic sleep patterns over the course of a night, with slow-wave sleep (formerly stages 3 and 4, now known as stage N3) predominantly during the first part of the night. Subsequent non-REM sleep is predominantly stage N2. Successive periods of REM sleep become longer as the night progresses. Stage N1 is a transitional stage between wakefulness and established sleep. Reprinted from Kryger, Roth, Dement (eds.), Principles and Practice of Sleep Medicine, 4th Edition, Carskadon MA, Dement WC, Normal Human Sleep: An Overview, p. 13–22, Copyright (2005), with permission from Elsevier.

pathway influencing arousal begins with the noradrenergic neurons of the locus ceruleus (LC), serotonergic cells of the dorsal and medial raphe, dopaminergic cells of the periaqueductal grey matter, histaminergic cells of the tuberomammillary nucleus, and peptidergic neurons in the lateral hypothalamus. This multi-source pathway extends to the lateral hypothalamic and basal forebrain areas, then on to the cortex. These monoaminergic neurons fire at their fastest rates during wakefulness, slow during non-REM sleep, and turn off during REM sleep. By the end of the century, the ventrolateral preoptic nucleus (VLPO) of the anterior hypothalamus was identified as a major inhibitory influence on the arousal system, with projections to all major components of this system in the hypothalamus and brainstem. VLPO neurons contain galanin and gamma-aminobutyric acid (GABA), both inhibitory neurotransmitters, and are innervated in return by the monoaminergic nuclei to constitute a feedback loop. The VLPO, including core and extended areas of cells participates in the complex coordination of neuronal regulation of transitions between the states of wakefulness, non-REM sleep, and REM sleep. This complexity is governed by two influences known as the homeostatic and circadian processes that facilitate timing of the basic sleep-wake cycle. The homeostatic regulation of sleep (process S) constitutes the buildup of sleep need, or propensity, generated by prior wakefulness. It can be measured by the buildup of adenosine which influences the VLPO, and also retrospectively by the intensity of slow wave EEG activity that increases in non-REM sleep proportional to the duration of prior wakefulness. Other substances including tumor necrosis factor alpha (TNF-α), nitrous oxide, and interleukins (including IL-1, IL-6) have been shown to influence the expression of sleep (15). The second important regulatory influence is the circadian system, which produces a fluctuating wake signal originating in the suprachiasmatic nucleus (SCN) of the hypothalamus. This is the primary clock that increases and decreases its signal on a nearly 24-hour periodicity. Optimal sleep will occur when the homeostatic drive is maximal while the circadian wake signal is decreasing, and both processes are synchronized to the desired bedtime (16) (Fig. 37.4).

A basic theme for the understanding of all sleep disorders is that errors of sleep-wake state regulation result in dissociated and recombined elements of wakefulness and sleep that create the clinical pictures constituting insomnia; excessive daytime sleepiness; dissociated REM-sleep components like cataplexy, visual imagery, and sleep paralysis; and parasomnias like sleepwalking, sleep terrors, and the dream enactment of REM-sleep behavior disorder. The most compelling consequence of disruption of sleep duration or continuity is the corresponding increase of homeostatic sleep drive that can override the wake state and create unsustained attention, automatic behavior, and unwanted onset of frank sleep.

Thereby, sleep disorders present concerns of profound relevance to psychiatry. In many cases, they must be distinguished from primary psychiatric disorders. Conversely, primary insomnia, obstructive sleep apnea, narcolepsy, and certainly parasomnias may be misdiagnosed and inappropriately treated as psychiatric disorders, especially if the symptoms are particularly bizarre or violent, with emotional, cognitive, and/or perceptual aberrations. Most sleep disorders can be precipitated or worsened by stress as well as cause considerable distress and dysfunction in their own right. Sleep symptoms may be the presenting complaints in cases of other medical and neurological disorders that might come first to the attention of a psychiatrist.

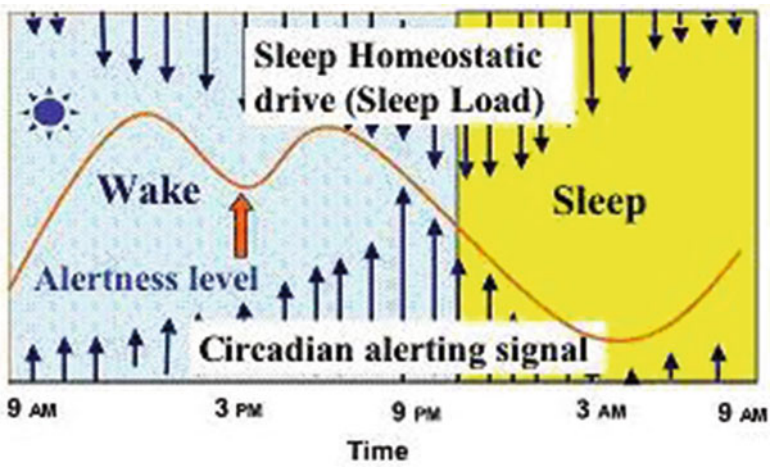


FIGURE 37.4 The two-process model of sleep–wake regulation. With ongoing wakefulness, the homeostatic sleep drive (process S) increases, reaching its maximum level as the circadian alerting signal (process C) diminishes. With ongoing sleep, the homeostatic drive dissipates, and wakefulness ensues as the circadian signal intensifies in the morning. Reprinted with permission from the American Academy of Sleep Medicine, Darien, IL.

37.3. Insomnia

37.3.1. Definition

Insomnia has traditionally been regarded as a symptom of difficulty with sleep onset or maintenance. Current psychiatric diagnostic formulation describes insomnia as dissatisfaction with sleep quality or quantity of sleep associated with difficulty initiating or maintaining sleep, and/or early morning awakening with inability to return to sleep causing significant distress or functional impairment as long as there is sufficient opportunity for sleep (1).

The International classification of sleep disorders, Second Edition (ICSD-2) defines general criteria for insomnia as (A) a complaint of difficulty initiating sleep, difficulty maintaining sleep, waking up too early, or sleep that is chronically nonrestorative or poor in quality. (B) This occurs when there is otherwise adequate opportunity and circumstances for sleep, and (C) there is some form of daytime impairment attributable to the nocturnal complaint, such as fatigue, malaise, impairment of attention, concentration, or memory; social or vocational dysfunction or poor school performance; mood disturbance or irritability; daytime sleepiness; motivation, energy, or initiative reduction; proneness for errors or accidents at work or while driving; tension, headaches, or gastrointestinal symptoms in response to sleep loss; and/or concerns or worries about sleep. Categories of insomnia include adjustment (acute) insomnia related to a particular stressor, paradoxical insomnia with no objective findings or daytime sequelae to support the nocturnal complaint, insomnia due to mental or medical disorders, inadequate sleep hygiene, and insomnia due to drug or substance use (17).

Closest to the insomnia disorder of DSM-5 are psychophysiological insomnia and idiopathic insomnia. The latter is distinguished by: (a) onset during infancy or childhood, (b) no identifiable precipitant or cause, and (c) persistence with no periods of sustained remission. The former must be present for at least 1 month, and include a conditioned, persistent sleep difficulty and/or increased arousal in the bed. There must be at least 1 of: (a) excessive focus on and elevated anxiety about sleep, (b) difficulty falling asleep at the desired time in the bed or for planned naps, but with no such difficulty during other monotonous activities when sleep is not planned, (c) better sleep in novel situations away from home, (d) mental arousal in bed with intrusive thoughts or the perception of inability to stop thinking that prevents sleep, and/or (e) increased muscular tension in the bed with the perception of inability to relax sufficiently to permit sleep. In all cases, the sleep disturbance is not better explained by another sleep, medical, psychiatric, neurological, or substance use disorder (17).

37.3.2. Epidemiology

The median prevalence of insomnia appears to be 35% in the general population with 10–15% prevalence of moderate or greater severity, suggesting a possible diagnosis of primary insomnia. Insomnia symptoms tend to be more frequent in women and increase with age for all people (18). If daytime consequences are included with insomnia symptoms, the prevalence ranges between 9–15%. Dissatisfaction with sleep quality or quantity is reported by 8–18% of people and actual insomnia diagnoses probably occur in about 6% of the population, remaining stable across age groups, in contrast to the increase of insomnia

symptoms (19). In spite of the prevalence of insomnia, the majority of sufferers do not seem to discuss it with their primary care physicians (20–22). In the elderly population, serious insomnia may affect at least 20–40% of people (23–26).

37.3.3. Clinical Picture

Patients with primary insomnia typically present an insomnia complaint coupled with corresponding daytime symptoms. They commonly describe increased arousal at bedtime. This may relate to pain, urinary frequency, respiratory symptoms, heartburn, limb restlessness, ambient stimuli in the bedroom, sleep-wake schedule, medication history, and use of caffeine, alcohol, and/or tobacco. Reports from bed partners add considerable descriptive history. A sleep-wake diary is very helpful to characterize the ongoing pattern and variability of insomnia. Patients typically find the bed and bedroom increasingly associated with wakefulness and make efforts to "try to sleep". This cognitive arousal leads to autonomic arousal and both will interfere with sleep onset. Dysfunctional beliefs about insomnia such as negative health risks, fear of death, loss of vitality, and/or loss of control over sleep causes many individuals to dread their nightly bed time and come to fear the ordeal of lying in bed without sleep (27). They endorse symptoms such as fatigue, poor motivation and concentration, mood disturbance, impaired psychomotor performance, and physical symptoms including headache, musculoskeletal difficulty, and gastrointestinal disturbance. In spite of these symptoms, patients do not fall asleep during the day, reflecting a generally hyperaroused state (28–30).

In the elderly population, the most frequent interferences with sleep are pain, cardiovascular disorders, pulmonary diseases, urinary problems, dementia or other neurological disorders, psychiatric disorders, and the effects of medications, drugs, and alcohol (18, 25, 31–37).

37.3.4. Case History

A 46-year-old married man complains of persistent difficulty falling asleep. He retires gradually earlier, currently at 9:00 pm, in an effort to get enough sleep to allow him to work effectively as an executive in a local industry. He fears that insomnia will permanently impair his productivity and potential for advancement. In bed, he becomes increasingly preoccupied with recollections from the previous day and projected activities for the coming week. He puts great effort into trying to disregard these thoughts and will toss and turn for up to 2.5 hours before falling asleep. This pattern tends to recur after he awakens at 3 am to urinate and then returns to bed. He awakens unrefreshed before his alarm sounds at 6:30 am. He reports fatigue but does not fall asleep, even if attempting to nap during daytime hours. He feels sluggish, endorses poor concentration at his work, and his mood has become depressed and irritable. Though zolpidem 10 mg has been very helpful during past bouts of insomnia, he prefers now to avoid medication to maintain his participation in civil aviation. He agrees to eliminate caffeine consumption, write in a daily journal before bedtime, and restrict his sleep to between the hours of 12 midnight and 6 am. Sleep onset and maintenance as well as daytime functioning begin improving over the next 4 weeks.

37.3.5. Laboratory Findings

Polysomnographic studies are rarely indicated for the evaluation of insomnia, and are reserved for cases unresponsive to therapy or if obstructive sleep apnea, parasomnias, or movement disorders are suspected (38). Quantitative electroencephalography has shown increased beta (fast frequency) activity and decreased theta and delta (slower frequencies) during sleep, suggesting increased cortical arousal (39, 40). Patients with insomnia have also been found to have increased physiological arousal, manifested by increased metabolic rate. Patients with paradoxical insomnia, previously called sleep state misperception, have lower metabolic rate than insomniacs but still more than normal sleepers (41). The sleep-wake diary can be supplemented by actigraphy, recorded by a wrist-worn movement monitor that can be worn for days or weeks to indicate periods of rest and activity. This is particularly helpful to distinguish paradoxical insomnia with clear periods of apparent sleep, and circadian rhythm sleep disorders when there is aberrant timing of sleep periods (42). Positron emission tomography (PET) performed with insomnia patients has shown greater global cerebral glucose metabolism during wakefulness and sleep, less decline with transition from wake to sleep in regions that promote wakefulness, and less relative metabolism in the prefrontal cortex while awake relative to normal control subjects (43). Further evidence suggests that insomnia relates to smaller than normal decline in metabolic activity in certain brain areas such as medial temporal cortex, thalamus, anterior cingulate, and brainstem arousal centers. This is especially prominent in the precuneus area of the frontoparietal cortex, which may influence the paradoxical perception of arousal during sleep that is characteristic of patients' descriptions of the experience (15) (Fig. 37.5).

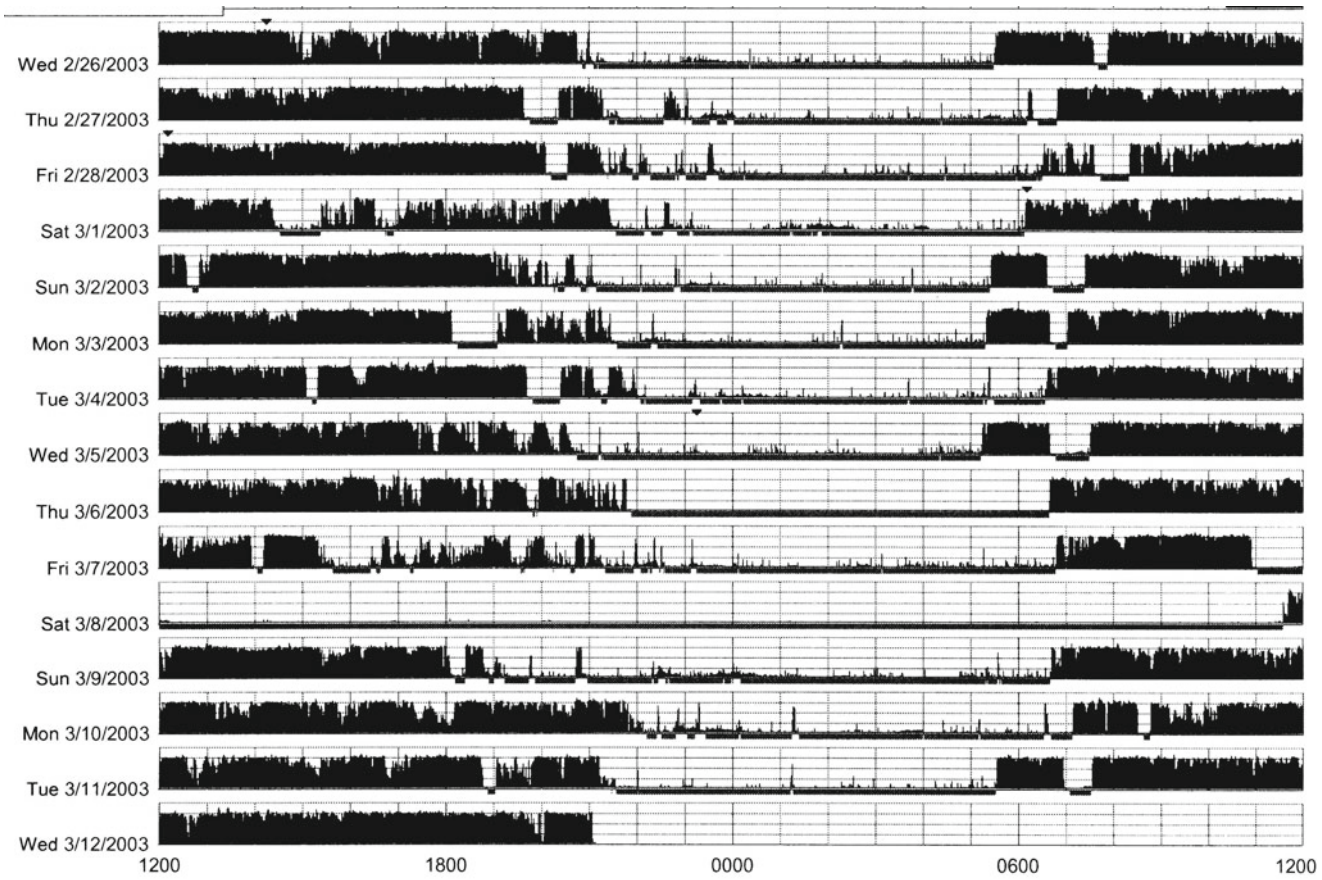


FIGURE 37.5 A wrist-worn activity monitor records movements in 1-minute time bins to display a representation of rest-activity (sleep-wake) cycling over a 2-week period. Note that during the period with absolutely no detectable movement, the device was not being worn. When coupled with a subjective sleep-wake diary, actigraphy can provide information from many successive days and nights.

37.3.6. Clinical Course

Short-term insomnia is often related to psychosocial stress, medical disorders and their treatment, or circadian rhythm sleep disorders. It is usually time-linked with the apparent precipitating events and treatment is focused on those causes. Some individuals are constitutionally predisposed to more fragile sleep capability. Most primary insomnia tends to be chronic, with longer than one-month duration (44–46). This disorder is related to similar predisposing and precipitating factors, but also perpetuating factors as patients come to anticipate and fear their inability to fall asleep or maintain sleep. Such perpetuating factors include violations of sleep hygiene by lying in bed trying unsuccessfully to sleep, using alcohol for sedation, using caffeine to enhance daytime functioning, and sleeping beyond a usual wake-up time in efforts to accumulate more sleep (47). Hence, there is a conditioned pattern of hyperarousal that develops in the situation where sleep is sought and desired. Some individuals report disturbed sleep onset and maintenance since early childhood, which constitutes idiopathic (childhood onset) insomnia (48). Insomnia has been associated with increased health care expenditure, social and occupational dysfunction, and impaired quality of life (49).

37.3.7. Differential Diagnosis

As described above, most insomnia is temporally related to precipitating factors. When it does not appear to be independent of another condition, it can be described as comorbid, which does not necessarily imply causality or association. Insomnia must be distinguished from voluntary insufficient sleep syndrome and must occur in spite of adequate opportunities for sleep. Many drugs have been implicated to cause acute insomnia, including methylxanthines, stimulants, steroids, some antihypertensives, and some antidepressants such as bupropion and SSRI drugs. Their role in chronic insomnia has not been systematically studied (44).

Circadian rhythm sleep disorders involve shifts in timing of sleep propensity but the sleep that occurs during these periods is unremarkable. The delayed sleep phase type often presents with a complaint of insomnia though the individual can easily fall asleep if not retiring to bed until the late hour when sleepiness becomes apparent. In that case, the person is not likely to awaken until after a normal sleep duration. This can lead to inability to conform to a desired work or social schedule (50).

37.3.8. Etiology

The etiology of primary insomnia is not clearly understood. A familial contribution is suggested by 35% of patients having a family history of some sleep disturbance, most frequently insomnia. This is more likely when onset for the index case is before age 40 and the predominant complaint is sleep onset difficulty (51). Abnormal elevations of urinary free cortisol reflecting elevated arousal are consistent with a sleep disturbance related to abnormal catecholamine metabolism (52). Not only is insomnia a ubiquitous symptom of depression, but also it appears from a few longitudinal studies that it is predictive of future incidence of depression (53–55). Exceptionally rare is a hereditary prion disease, fatal familial insomnia, resulting in neuronal loss and astrogliosis of the anterior medial thalamus and other structures. This produces severely disrupted sleep as well as dream enactment and other motor activation during sleep (56, 57).

Up to 40% of adults with insomnia in the general population (53) and about 75% of patients with insomnia in sleep center or primary care clinics have a psychiatric disorder (58). About 71% of these will have dementia, 69% depressive disorders, 61% anxiety disorders, and 32% alcohol dependence (59). Polysomnographic studies of depression have shown diminished slow-wave sleep (stage N3), frequent nocturnal arousals and awakenings as well as reduced time between sleep onset and the first REM period (60, 61). By PET imaging, there appears to be less cortical and thalamic deactivation in depressed patients compared to healthy controls as they undergo the transition from wake to sleep. This suggests a degree of cerebral metabolic activation that may be associated with the nonrestorative sleep complaint of patients with depression (62).

37.3.9. Treatment

37.3.9.1. Non-Pharmacological Therapy

Cognitive behavior therapies (CBT) include techniques that have been demonstrated to counter the perpetuating factors responsible for continuing chronic insomnia. Various techniques are combined into an individualized program, which can be administered by psychologists, psychiatrists, nurses, and primary care physicians during an average of 3–10 sessions. A traditional element is stimulus control therapy, which acknowledges the bedroom as a conditioned stimulus for wakefulness where insomniacs can remain for extended periods trying to sleep. Leaving the bedroom if not sleeping decreases the impact of this learned association. The bed is reserved for sleep or sexual activity and nothing else (63, 64). Another component, sleep restriction therapy, calls for reducing the time spent in bed in order to diminish wakefulness during that period and increase the homeostatic sleep drive which derives from partial sleep deprivation (65). Relaxation training can be added to decrease arousal (66). These strategies are combined with a cognitive, psychoeducational approach to challenge feared consequences of sleep loss, revise expectations for normal sleep, and reinforce principles of sleep hygiene such as regular sleep scheduling and modulation of caffeine use (67, 68). CBT for insomnia (CBT-I), is clearly effective for reduction of sleep onset latency and subsequent awakenings in at least 50% of patients (66, 69–71). Benefits appear to be sustained in studies of up to a year in duration and may be more enduring yet, when hypnotic medication has not been prescribed (66, 72–74). Longer duration outcome studies are needed for all insomnia remedies and it is remarkable that currently available evidence covers such short intervals in the case of a typically longstanding, chronic condition. Brief forms of CBT-I have been developed to increase its clinical availability and internet-based programs are also coming into use (75–77)

37.3.9.2. Pharmacological Therapy

37.3.9.2.1. Hypnotic Drugs

Pharmacotherapy has been used for insomnia since alcohol, chloral hydrate, and barbiturates have been known. Currently, the principal hypnotic agents are the benzodiazepines (BZ), benzodiazepine receptor agonists (BZRA), and the melatonin agonist, ramelteon. The former two groups act at the BZ receptor site on the GABA-A receptor complex, closing the chloride channel and diminishing neurotransmission.[1] The BZ's currently approved in the United States for treatment of insomnia include flu-

[1]Editor's note: the orexin receptor antagonist suvorexant at an initial dose of 5 mg/day with a usual dose range of 5-20 mg/day has been approved by the FDA for the treatment of insomnia.

razepam, triazolam, quazepam, estazolam, and temazepam. BZRA's include zolpidem, zaleplon, and eszopiclone. These drugs are all rapidly absorbed and variably metabolized and excreted. There is a new sublingual preparation of zolpidem 1.75 and 3.5 mg that is more rapidly absorbed and eliminated, which may be considered for middle of the night use if at least 4 hours remain before morning awakening. Two BZ's, flurazepam and quazepam, have long durations of action with elimination half lives ($t_{1/2}$) of 48–120 hours. The BZRA's include an ultra short duration drug, zaleplon with $t_{1/2}$ 1.0 hour. All the others are of intermediate (temazepam, estazolam, eszopiclone with $t_{1/2}$ of 5–15 hours), and short duration (triazolam, zolpidem with $t_{1/2}$ of 1.5–5 hours). As a rule, the longer duration BZ's can cause hangover sedation and should be reserved for patients requiring anxiolytic effect by day. These and the intermediate duration drugs may be more useful for patients with sleep maintenance insomnia over the course of the night. Zaleplon, typically cleared within 4 hours, may be taken during the night if wakeful activity is not anticipated during that interval.

In normal sleepers, BZ's tend to decrease sleep onset latency, wake after sleep onset, stage N1 sleep, stage N3 sleep, and REM. They tend to increase total sleep time, sleep efficiency, stage N2 sleep, EEG fast activity, and latency to the first REM period. When studied exclusively in insomniacs, predominant effects are increased total sleep time and reduced stage N3. Zolpidem has very little effect on the structure of polysomnographically (PSG) measured sleep other than shortening latency and increasing continuity (78). In a PSG study of insomnia treated with zolpidem, drug treatment lowered sleep latencies to persistent sleep from 61.9 ± 6.7 (SD) to 23.7 ± 2.3 minutes (79).

Most studies of these agents have been conducted over short periods, typically up to 8 weeks, with the exception of intermittent dosing of zolpidem over 12 weeks, and nightly eszopiclone during a 6-month extension. These all document continuing efficacy without development of tolerance. Because most primary insomnia is chronic, physicians are apt to treat it with long-term use of hypnotic drugs though there are no studies yet providing citable evidence (45, 80–82).

Many side effects are related to elimination half-life. Withdrawal effects including rebound insomnia (i.e. worse than pre-treatment) are typically not seen with long duration drugs and increase with decreasing half life BZ's (83–85). This is a transitory 1–3 night phenomenon when it occurs. It is not appreciably associated with BZRA's. Anterograde amnesia can be problematic and typically associated with the shorter duration BZ's and BZRA's. It is likely dose-related and has been particularly noted with triazolam (86, 87), but can occur with any of them. Zolpidem has been associated with unusual sleepwalking and sleep-related eating (88, 89), as have risperidone and olanzapine (90, 91). It is possible that the perception of continuous, refreshing sleep is, in part, related to the anterograde memory inhibition of BZRA's (92). With evidence of longer half-life of elimination in women, a recent FDA recommendation has been promulgated for maximum dosage of zolpidem 5 mg and zolpidem extended release preparation 6.25 mg for females. These doses are also to be considered for all patients in view of the possibility of morning hangover sedation that can impair performance such as for driving (93).

Though acute BZ effects of memory impairment are clear, there have been some studies suggesting an association between exposure to these drugs and development of dementia. A large long term cohort study of community dwelling French subjects 65 years of age and older has been recently reported. Use of BZ drugs initiated during the follow-up period was associated with increased risk of incident dementia comparable to the rate of dementia in subjects who ever used BZ, with odds ratios about 1.5 compared with those who never used them (94). Insomnia and anxiety are common in the elderly, and the latter can also be an early manifestation of cognitive impairment as can behavioral changes such that the indications for BZ use could lead to unwitting selection bias. This possible confound as well as the long prodromal course of eventual dementia makes the association with BZ drugs still unclear (95).

Ramelteon is a melatonin-1 and -2 receptor agonist that is available in 8 mg dosage form. It has $t_{1/2}$ of 2–5 hours and no evidence of rebound insomnia, tolerance, or amnesia. It has been reported to benefit primary insomnia in younger and older adults (96, 97). Long-term efficacy may not be clearly established, especially for older patients. A systematic meta-analysis has reported to show subjective reduction of sleep latency only for patients 18–64 years of age, though polysomnographic sleep latency and total sleep time appear significantly improved (98, 99). Animal data has documented efficacy for re-entrainment of circadian rhythm sleep disorders (100).

37.3.9.2.2. Other Drugs

Many other drugs have been prescribed to treat insomnia. A large study based upon a nationally representative Physician Drug and Diagnosis Audit of approximately 3400 physicians during 2002 cites "drug occurrences" in millions for trazodone (2.7 m) as the most frequently prescribed agent for use as "hypnotic", to "promote sleep", or to "sedate night". This frequency of prescriptions is 32% more than for zolpidem (2.1 m), the second ranking drug, followed by amitriptyline (0.8 m), mirtazapine (0.7 m), quetiapine (0.5 m), olanzapine (0.2 m), hydroxyzine (0.3 m), doxepin (0.2 m), cyclobenzaprine (0.2 m), and diphenhydramine (0.2 m). Only four of the top sixteen drugs were FDA approved for insomnia, not including clonazepam (0.4 m),

alprazolam (0.3 m), and lorazepam (0.3 m) that are not so approved but which also appeared. In spite of the low level of evidence for hypnotic efficacy of antidepressants, the author suggests that their favored status relates to product label limitations on duration of use of hypnotic drugs, their DEA schedule IV status, and their perceived liability for abuse and dependence. There is no substantial support in the literature to document such high risk (101, 102).

Trazodone, a weak specific serotonin reuptake transporter inhibitor (SSRI), also inhibits 5-HT-1A, -1C, and -2 receptors. It is a moderate inhibitor of histamine-H1 receptors but is not anticholinergic (103). While trazodone may increase stage N3 sleep, it has little effect on REM. While it may diminish sleep onset latency, increase total sleep time, and increase sleep efficiency in some studies of normals or depressed patients, these effects were limited to a single week for insomnia patients (104–108).

Selective serotonin reuptake inhibitor (SSRI) agents are among the most widely prescribed antidepressants. They have long been known to suppress REM sleep. They also increase sleep fragmentation with awakenings and stage shifts (109–111). A striking finding in patients treated with SSRI's is persistence of slow eye movements well into consolidated non-REM sleep. This is of unknown clinical significance though it indicates an enduring neurophysiological response from prior exposure to SSRI drug. This can continue even long after the drug has been discontinued (112).

The tertiary amine tricyclic antidepressants (TCA's), doxepin and amitriptyline, inhibit histamine, acetylcholine, alpha-1, and alpha-2 adrenergic receptors. Antihistaminic activity mediates sedation, while anticholinergic activity contributes to the inhibition of REM sleep seen with these drugs (113). Doxepin, with especially potent affinity for the H1 receptor, has been marketed in low 3 and 6 mg dosage forms for treatment of insomnia. Trimipramine does not appear to affect REM sleep. TCA's do have documented capacity to reduce sleep latency and improve sleep efficiency in normals and depressives, but only limited data show improved sleep efficiency for primary insomnia (114–118).

In a large study of major depressives treated with nefazodone, a potent 5HT-2 inhibitor, there was a small but statistically significant increase in sleep efficiency and decreases in number of awakenings and wake time during sleep. Most notable is the absence of REM inhibition (119).

Mirtazapine is a potent antihistamine that also antagonizes 5HT-2, alpha-1, and alpha-2 noradrenergic receptors. It appears to decrease sleep latency and increase stage N3 sleep in healthy adults though not as clearly in depressed patients. Its sleep-favoring effects seem to be more potent at low doses where antihistaminic effects may predominate (119–121).

Other antihistamines such as diphenhydramine that can act centrally to mediate sedation do not appear to be potent inducers of polysomnographic sleep. There also appears to be rapid tolerance to this effect. Coupled with anticholinergic, cognitive, psychomotor, and anorectic side effects, diphenhydramine is a less ideal hypnotic in spite it's 16th place frequency of use in 2002 (101, 108, 122–125).

Ever since the days of sedating phenothiazines, sedating neuroleptic drugs have been used to enhance sleep. This is particularly useful during treatment of schizophrenic and affective psychoses, when control of insomnia is an integral component of acute therapy. More recently, atypical neuroleptics have been used in the same manner. Few studies, however, address the use of these drugs for insomnia and there is no conclusive evidence for their use in its treatment (126).

Clozapine is a 5HT-2A, -2C, -6, and -7 receptor antagonist as well as a 5HT-1A partial agonist, which may relate to its tendency to increase non-REM sleep. In a study of 36 schizophrenic patients, clozapine was associated with total sleep time of 432 ± 50 minutes in $n = 12$, compared to 409 ± 40 minutes in the $n = 10$ classical neuroleptic group and 361 ± 59 minutes in 14 drug-naïve patients. Sleep latency was 26 ± 34 minutes in the clozapine group, 13 ± 17 minutes in the classical neuroleptic group, and 56 ± 55 minutes in drug-naïve patients (127). Also in schizophrenic subjects, clozapine was associated with improved sleep continuity and increased stage N2 sleep, but no significant change of sleep latency from the beginning of therapy through at least seven weeks of treatment (128). In another study of bipolar and schizoaffective disorders, clozapine was found to be associated with a lengthening of sleep latency but data from this study also indicates that it is primarily a non-REM sleep enhancer with increased total sleep time and subjective reports of restedness (129).

Quetiapine is also a strong 5HT-2 antagonist as well as antihistaminic, antidopaminergic, and antiadrenergic agent. In a double-blind, placebo-controlled study of quetiapine in healthy subjects, doses of 25 and 100 mg were associated with significantly shortened sleep latencies, from 15.4 ± 12.5 minutes on placebo to 8.2 ± 5.2 minutes on 25 mg and 7.4 ± 5.7 minutes on 100 mg. Total sleep time increased from 433 ± 16 minutes (placebo) to 450 ± 7.4 (25 mg) and 446 ± 26 minutes (100 mg). Similar benefits were noted during a night of acoustic stress. There was an increase of periodic leg movements and decreased stage REM percent with the 100 mg dose (130).

Olanzapine, another potent 5HT-2A and -2C antagonist, also has affinity for muscarinic cholinergic, alpha-1 adreno-, and histamine H1 receptors. It is believed that the 5HT-2C receptor is involved in the regulation of non-REM slow-wave sleep, which was increased substantially in a study of healthy male adults and SSRI-resistant depressed patients (131, 132).

Risperidone, also a 5HT-2 blocker, has been shown to decrease REM sleep duration in normals and treatment-resistant depressed patients in whom total and stage 2 sleep increased. It did not affect REM latency (133).

37.4. Movement Disorder: Restless Legs Syndrome

37.4.1. Definition

Though categorized as a sensorimotor or movement disorder, restless legs syndrome (RLS) is a frequent cause of difficulty falling asleep. Described extensively by Ekbom (134) it remains an interesting and challenging clinical problem. With increasing understanding of its pathophysiology and literary heritage, it has been newly designated as Willis-Ekbom Disease (WED), and it is now included in DSM-5 where it is still designated as RLS. Diagnostic features have been elucidated by an international RLS study group and the ICSD-2 diagnostic criteria for adults include: (A) urges to move the legs, usually due to or associated with discomforting sensations in the legs; (B) the urges or sensations begin or worsen with rest or inactivity; (C) they are partially or completely relieved during movement of the limbs; (D) they are predominantly or exclusively present during the evening or night hours; and (E) the symptoms are not related to any other sleep, medical, neurological, psychiatric disorder, or to medication or substance use disorders (17).

37.4.2. Epidemiology

WED appears to be increasingly common with a prevalence estimated to be 10–15% of the general population, more frequently in women than men (135–139). It is found in 20% of pregnant women (140, 141), 20–62% of patients with chronic renal failure treated with dialysis (142, 143), and 5.2% of patients with polyneuropathy (144).

37.4.3. Clinical Picture

The core feature of this disorder is the strong or irresistible urge to move the legs, most typically in response to sensations that are not easily described and/or painful, such as “creepy-crawly”, “like bugs marching in my legs’, or “like bubbles in the veins”. These may occasionally extend into the trunk and upper extremities, and can be extremely uncomfortable. They are always worse in the evening and night, though they may emerge during relaxed wakefulness by day. Some patients will experience involuntary jerking of limbs, and most will have continuing repetitive, periodic movements of their limbs during sleep. At times, individuals will need to arise and walk about. Hence, this disorder can impact negatively on sleep onset as well as maintenance. Symptoms can vary in frequency from nightly to intermittent (145, 146).

37.4.4. Case History

A 33-year-old woman complains of difficulty falling asleep for many years. This worsened during each of her 2 pregnancies and improved for a period of time when iron supplementation was prescribed during the month preceding her last delivery and the subsequent 3 months. She was said to have suffered “growing pains” during adolescence and remembers similar but milder leg discomfort at night during her youth. She retires to bed around 10 pm and, with relaxation, her legs feel increasingly “antsy” and she cannot find a comfortable position without stretching and moving them, occasionally placing a pillow between her knees. Frequently, she’ll get up and walk in circles around her living room before returning to bed. She falls asleep after 60–90 minutes and her husband says that her legs continue to move at intervals while she is asleep. He must leave the bed and sleep elsewhere about twice weekly because of this. She reports similar discomfort during attempted late afternoon naps but with less intense need to move. She has requested help because of increasing daytime fatigue, irritability, and worry about her ability to care for her children. Neurological examination is unremarkable. Mood is mildly depressed but without any history or family history of depressive disorder. Hemoglobin is 14.1 and serum ferritin is 107 micrograms per liter. After beginning pramipexole 0.125 mg taken 2 hours before bed time and increasing to 0.375 mg, she reports improvement of sleep onset and daytime symptoms.

37.4.5. Laboratory Findings

There are often no clinical laboratory findings unless peripheral iron deficiency is present. Serum ferritin, a measure of iron storage, can be reduced in cases of blood loss such as menorrhagia, gastrointestinal bleeding, and frequent blood donations. Concentrations below 45 micrograms per liter can be associated with increasing severity of WED (146–150). Polysomnographic studies of sleep in patients with WED demonstrate periodic leg movements during sleep (variably associated with EEG arousals)

and initial wakefulness in 80–90% of cases (151). Another diagnostic procedure is the Suggested Immobilization Test (SIT), which monitors leg movements polygraphically with the patient seated upright on a bed at usual bedtime. A total of more than 40 periodic leg movements during wakefulness supports the diagnosis of WED (152). Actigraphic monitoring of periodic leg movements has also been utilized (153).

37.4.6. Clinical Course

WED may occur at all ages and can be misdiagnosed as "growing pains" in children (154, 155). When beginning before age 45, symptoms progress slowly from an intermittent to a more frequent pattern and may become daily by 40–65 years of age. Late onset WED progresses much more rapidly. Symptoms typically begin in the feet and legs but may progress, in some patients, to the trunk and upper extremities. They have a marked circadian pattern of evening and nocturnal worsening. They may occur by day, especially when the patient is inactive such as during long periods of enforced seating in a vehicle, theatre, or work setting (135, 156). There is accumulating indication that the intermittent arousal associated with periodic leg movements might be associated with cardiovascular risk (157).

37.4.7. Differential Diagnosis

Traditional neuroleptic medications antagonizing dopamine receptors may induce akathisia resembling WED but with more generalized body restlessness and absence of prominent circadian variation. The neurological condition of painful legs and moving toes is also not diurnally variable, nor is it associated with an urge to move. Discomfort related to positional effects of the body on a supporting surface includes no urge to move and is resolved by change of position. Sleep starts, or hypnic myoclonia, are normal involuntary movements limited to the moment of transition between wake and sleep and with no urge to move. They can be associated with bursts of visual and auditory sensations in some individuals. Sleep-related leg cramps involve actual muscle spasm and require stretching and recovery time rather than simple movement for improvement. Though some WED is experienced as painful, movement as a response to pain from various sources is not typically based upon an urge to move per se (17). Insomnia with anxiety and psychomotor agitation is likewise not associated with an urge to move or relieved by it.

37.4.8. Etiology

There is a genetic predisposition with a familial distribution of WED, which occurs 3–6 times more frequently in first degree relatives of affected subjects than in the general population. An autosomal dominant transmission has been described in some families. There tends to be more genetic contribution with younger age of onset (17, 151, 158). The pathological basis of WED is likely related to deficient brain iron acquisition by the neuromelanin cells in the substantia nigra. Decreased iron availability in these cells may compromise dopaminergic function by limiting synthetic enzyme activity or the expression of dopamine transporters or receptors (159). As noted above, WED occurs frequently in patients with iron deficiency, severe renal disease and pregnancy. Peripheral neuropathy is often associated with WED, and its associated pain may contribute to the urge to move. It can also emerge in cases of spinal cord injury (160). When measured, cerebrospinal fluid ferritin levels have been 65% lower than normal peripheral levels in patients with WED suggesting specific brain iron deficiency (161). Decreased density of dopamine D-2 receptors have been observed in the striatum of WED patients by PET and single photon emission computerized tomography (SPECT) imaging (162–164). Many sedating antihistamines, numerous antidepressant drugs (other than bupropion with its dopaminergic property), and dopamine antagonists will precipitate or worsen WED (17, 165).

37.4.9. Treatment

The only currently FDA approved drugs for treatment of moderate to severe WED are the dopamine agonists ropinirole, pramipexole, and rotigotine as well as the alpha-2 delta ligand gabapentin enacarbil. Many more drugs are used in off-label strategies. For mild disorders, some non-pharmacological approaches such as compression stockings, near-infrared light treatment, and exercise have been reported (166). A treatment algorithm has been proposed, based upon the frequency of WED symptoms (146). For mild, intermittent WED, non-pharmacological strategies are useful. If appropriate, mentally alerting activities may reduce daytime symptoms. Trial restrictions of caffeine, nicotine, and alcohol may be instituted and selected drugs such as antidepressants may be eliminated if safely possible. Replacement of iron should be prescribed if serum ferritin

is < 20 micrograms per mL and considered if ferritin is < 50, which has been associated with worsening of WED (147, 149). The initial pharmacological strategy for intermittent symptoms is typically prescription of a dopaminergic agent. The initial choice could be carbidopa/levodopa, 25 mg/100 mg as needed, but alternatives include dopamine agonists pramipexole 0.125 mg, or ropinirole 0.5 mg taken 1 (ropinirole) or 2 (pramipexole) hours before bedtime as needed and titrated further as indicated. Open label polysomnographic studies of pramipexole and a large double-blind placebo controlled study of ropinirole document effectiveness of these dopamine agonists for treatment of subjective (insomnia) and objective (limb movements) features of WED. Other options include low-potency opioids propoxyphene or codeine, opioid agonist tramadol, BZ's temazepam or triazolam, or BZRA's zolpidem or zaleplon, which may be considered as needed (167–170).

For WED occurring nightly, regularly administered therapy is needed and includes the same non-pharmacological techniques as well as nightly dopamine agonist, gabapentin, or low-potency opioids. Refractory symptoms may develop with inadequate or decreasing benefit from dopamine agonists, intolerable side effects, and/or augmentation of WED symptoms causing occurrence earlier in the day or more proximal in the body. For these challenging cases, change to gabapentin or a different dopamine agonist is considered or a second agent from the list above can be added. But, if there is prominent augmentation associated with the dopamine agonist, the more advisable course is to taper and discontinue the drug and change to an agent of another category. An important side effect of dopamine agonist therapy is the emergence of impulse control disorders such as compulsive gambling, buying, and sexual behavior, which have been reported in patients with Parkinsons Disease on these drugs. All patients treated with them must be warned about this risk, which can occur in as many as 4–8% of patients (171–173). When there is inadequate response or failure with dopamine agonist or alpha 2 delta ligand therapy, change to a high potency opioid or tramadol may be needed (146). In severe cases of WED, both associated with prominent leg pain or not, methadone therapy on a long-term basis may be required as monotherapy or combined with a dopaminergic agent (174).

37.5. Obstructive Sleep Apnea

37.5.1. Definition

Among the breathing-related sleep disorders in the DSM-5 are the respiratory drive disturbances known as central sleep apnea syndromes related to neurological and cardiovascular disorders, respiratory depressant drugs (e.g., opioids), and high altitude environments. Sleep may also be disturbed by non-obstructive alveolar hypoventilation in cases of pulmonary disease, such as lower airway obstruction, as well as neuromuscular and chest wall dysfunction. The most common breathing-related sleep disorder is obstructive sleep apnea (OSA). Now formally defined in the DSM-5, it is designated as a condition resulting in excessive sleepiness or unrefreshing sleep, with particular polysomnographic findings, and not accounted for by another mental disorder, substance, or medical condition (1).

The ICSD-2, defines obstructive sleep apnea as marked by at least 1) complaints of unintentional sleep episodes during wakefulness, daytime sleepiness, unrefreshing sleep, fatigue, or insomnia, or 2) awakenings from sleep with breath holding, gasping, or choking, or 3) bed partner reports of loud snoring, breathing interruptions, or both during the patient's sleep. In all cases, there must be polysomnographic evidence of five or more scoreable respiratory events per hour of sleep. These respiratory events are apneas or hypopneas (10 second periods of complete or partial cessation of air flow) if there is evidence of respiratory effort during all or a portion of each event, and respiratory effort-related arousals (RERA's), EEG arousals associated with crescendo snoring or decreased oronasal air flow. In either case, the disorder may not be better explained by another current sleep disorder, medical or neurological disorder, medication use, or substance use disorder. Alternatively, the diagnosis may be applied in the absence of symptoms if there is polysomnographic evidence of fifteen or more of these scoreable events per hour of sleep (17).

37.5.2. Etiology

The basis of OSA is sleep-disordered breathing (SDB) caused by the collapse of the pharyngeal airway space when negative intraluminal pressure caused by the diaphragm during inspiration overcomes the capacity of the throat dilator muscles tensing the palate and holding the tongue forward to hold the space open. Additional pressure on the airway from soft tissue and bony structures also adds force to constrict the airway. The more soft tissue relative to the size of the bony compartment (e.g., obesity), the more the airway space is compromised by the anatomical contribution to extraluminal pressure that can collapse the airway. Craniofacial abnormalities such as small mandible, macroglossia, retrognathia, and acromegaly also predispose to OSA (175). Airway size is further reduced in the presence of obstructing tissue such as tonsils and adenoids. Body position during sleep can influence this by force of gravity. When sleep occurs, there is less dilator muscle response to negative

pressure of inspiration. Further, lung volume diminishes during sleep and this decreases traction on the airway, creating further vulnerability (176). Obesity is common and a linear correlation has been established for neck girth and severity of OSA (177, 178).

If there is minimal airway collapse, snoring alone can occur with tissue vibration but no alteration of airflow. With more compromise of airway patency, there can be varying degrees of air flow limitation and increased inspiratory effort that can lead to RERA's. These may be inferred from a pattern of crescendo snoring on successive preceding breaths, characteristic flattening pattern on a nasal pressure monitor of air flow during sleep, or from increased intrathoracic pressure on esophageal manometry which is not frequently utilized in conventional PSG. These events typically interrupt sleep continuity without significant drop in tidal volume or change in oxyhemoglobin saturation as measured by transcutaneous colorimetric oximetry. Further increasing of airway obstruction can compromise actual airflow and result in partial (hypopnea) or complete (apnea) interruption. These events result in lowering arterial partial pressure of oxygen (PaO_2), leading to desaturation of oxyhemoglobin.

Such sleep fragmentation and intermittent hypoxia following these events may also contribute to development of hypersomnia, the hallmark symptom of OSA. The apnea-hypopnea index (AHI), or hourly frequency of these events, is the most typical metric cited in published studies. The term, respiratory disturbance index (RDI) is not often well defined and may refer to AHI or to the rate of all three types of obstructive respiratory events. AHI of 5–15/hour would generally be considered as mild, 15–30/hour, moderate, and ≥ 30, severe OSA. When these events occur with clinical symptoms, the condition is designated as obstructive sleep apnea syndrome (OSAS).

37.5.3. Clinical Picture

The clinical presentation of OSAS includes reports of snoring, often with apneas witnessed by bed partners, and excessive daytime sleepiness (179). Sleepiness refers to the tendency to fall asleep in contrast to fatigue during intact wakefulness. It can be assessed by a questionnaire such as the Epworth Sleepiness Scale though this has modest correlation with the AHI (159). Sleepiness symptoms can include falling asleep ("dozing") during activities such as sitting and reading, watching TV, sitting inactive in a public place, as a passenger in a car for 1 hour, lying down to rest in the afternoon, sitting while talking with someone, sitting quietly after lunch without alcohol, and in a car when stopped for a few minutes in traffic (180, 181). The degree of objectively measured sleepiness (presumably related to sleep fragmentation) varies with the AHI within individuals (182). The multiple sleep latency test (MSLT) has demonstrated evidence of this with mean latencies to sleep onset during four or five nap opportunities of $6.8+4.2$ minutes, clearly less than 11.6 ± 5.3 minutes following therapy (183). Still, however, only 35% of individuals with AHI ≥ 30 may report symptomatic sleepiness (182). The most dramatic negative outcome of excessive sleepiness is drowsy driving (184–186). While there is evidence that drivers with OSA have higher accident rates and less driving-based cognitive performance than control subjects, the statistical relationships with AHI are not strong (187–193). A validated questionnaire has shown utility for diagnosing OSAS based upon presence and frequency of snoring, daytime sleepiness or fatigue, and history of obesity and hypertension. It predicts a high risk of OSA when symptoms are persistent and frequent in any two of these three domains (194).

Psychiatric disorders must also be considered in the clinical evaluation of OSA. Individuals with major depressive disorder have a fivefold higher likelihood of having DSM-IV defined breathing-related sleep disorder than non-depressed persons, even when controlled for obesity and hypertension. About 20% of individuals with one of these disorders appear to have the other as well (195). A longitudinal study has shown that, as OSA worsens from minimal to mild, the likelihood of developing depressive symptoms by the Zung depression scale increases by nearly 1.8-fold. When compared to normals in that study, incidence of depression increased by factors of 2 for mild and 2.6 for moderate or worse sleep-related breathing disorder (196). In a cross sectional study at a large VA medical center, patients with OSAS had statistically significantly increased prevalence of a number of psychiatric disorders when compared to patients without OSAS. Odds ratios were 2.67 for depressive disorders, 16.67 for anxiety disorders, 11.85 for posttraumatic stress disorder, 5.13 for psychotic disorders, 4.06 for bipolar disorder, and 2.13 for dementia (197). The fatigue associated with comorbid depression may itself account for some of the symptomatology of OSAS when the two conditions overlap (198–200). This relationship is supported by the improvement of depressive symptoms with treatment of OSAS (201–203).

Neuropsychological disturbances have been reported in OSAS. Deficits of attention, concentration and vigilance, manual dexterity, visuomotor skills, memory, verbal fluency, and executive function have been documented and appear to be mildly or moderately associated with severity measures by PSG. Daytime sleepiness as well as nocturnal, accumulated intermittent hypoxemia probably contributes to problems with memory, problem-solving, and executive functioning (187, 204). Vigilance and attentional capacity deficits most resemble the effects of chronic partial sleep loss (205, 206). A large meta-analysis has shown untreated OSA to have no significant effect upon intellectual and verbal functioning but significant effects on vigilance and executive functioning. Memory was less uniformly affected. Fine motor coordination and drawing are more vulnerable to the effects of OSA than tests of fine motor speed or visual perception (207).

37.5.4. Epidemiology

Widely cited information about epidemiology of OSA comes from a number of groups including the Wisconsin Sleep Cohort and the multi-center longitudinal Sleep Heart Health Studies that have been underway for many years. These data, generally based upon internally consistent definitions and methodologies, permit the conclusion that 20% of normal weight Caucasian adults in the US have AHI of at least 5/hour and 6.7% have AHI of at least 15/hour. Up to 5% of adults are likely to have the OSAS with respiratory obstruction, daytime sleepiness, and/or other symptoms. Prevalence among women is about half of this, though their risk increases with postmenopausal status. Predisposing features include obesity, advancing age, and snoring (208–211).

37.5.5. Case History

A 48-year-old single man with chronic schizophrenia is noted to fall asleep during group sessions at his psychiatric day treatment program. His weight had increased over a decade to 280 pounds for a body mass index of 39.75. He reports difficulty remaining awake whenever sedentary and has become drowsy when driving though denying any accidents. He is the sole driver in the home that he shares with elderly parents and a chronically ill sister. He reportedly snores, snorts, and gasps during the night but there is no bed partner to describe any witnessed apneas. He is treated for severe hypertension, congestive heart failure, gastro-esophageal reflux disorder, non-insulin dependent diabetes, and schizophrenia. On polysomnography, he is found to have apnea-hypopnea index = 80/hour with oxyhemoglobin desaturation nadir of 78%. Continuous positive airway pressure at 18 cm is effective but he is unable to tolerate the mask in spite of extensive attempts at desensitization and numerous mask configurations. Titration with bi-level positive airway pressure is tried but is likewise rejected by the patient. He then undergoes surgical revision of the soft palate with removal of the uvula (uvulopalatopharyngoplasty), again without improvement. Ultimately, he is treated with tracheostomy and experiences marked improvement in nocturnal sleep and daytime alertness.

37.5.6. Laboratory Findings

PSG in an attended laboratory situation is still the standard means of evaluating breathing during sleep. Typical obstructive events are recorded as in the Fig. 37.6. More limited diagnostic instruments are being developed and have demonstrated utility that can be useful for cases with high pre-test probability in patients who cannot be studied in a laboratory. These include cardiopulmonary monitors of respiration only, portable PSG, and peripheral arterial tonometry (PAT), which measures autonomic manifestations of respiratory obstructive events (212, 213).

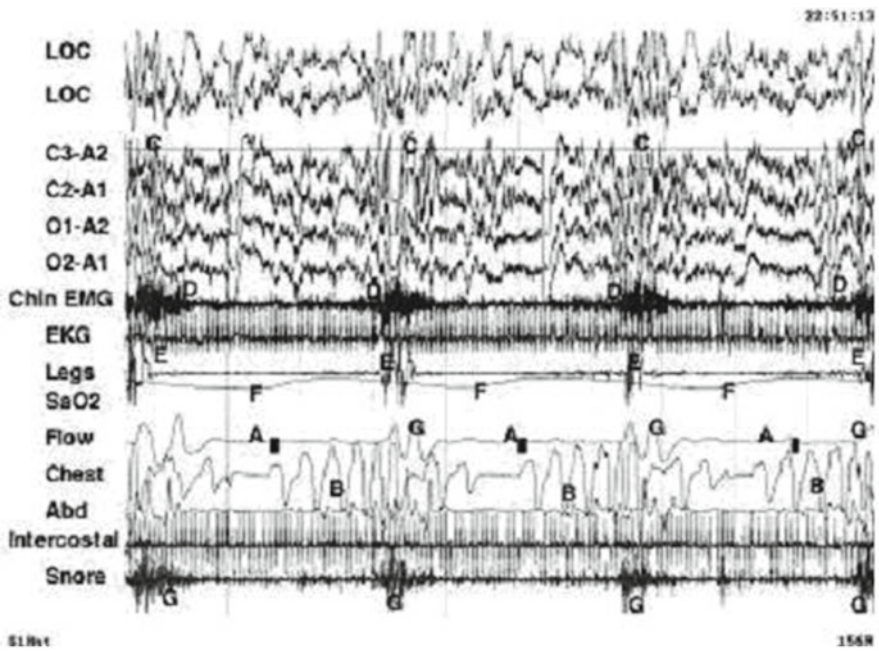


FIGURE 37.6 A 2-minute window demonstrates four obstructive apneas, with cessation of air flow (A) in the presence of persisting thoracic and abdominal manifestations of respiratory effort (B). These events are followed by EEG arousal (C) and bursts of chin muscle tone (D), leg movements (E), desaturations of oxyhemoglobin (F), and resumption of air flow with snoring (G).

The overall total of apneas, hypopneas, and RERA's per hour describes the rate of sleep fragmentation relevant to subsequent daytime dysfunction (214). Formerly, the disruption of sleep caused exclusively by RERA's was known as upper airway resistance syndrome (UARS) and recognized as a cause of daytime sleepiness (215). It is now subsumed under the diagnosis of OSAS.

37.5.7. Clinical Course

OSA can begin in infancy and may be related to craniofacial anatomy and nasal airway deficiency (216). In children and adults, adenotonsillar hypertrophy can often account for the emergence of the disorder. Typically, OSA increases with age though elderly individuals may have fewer daytime symptoms than middle-aged counterparts (217). Over an 8-year follow-up study in the Wisconsin Sleep Cohort, the AHI increased in all groups including normals but most prominently in those with obesity and the habitual snoring (211).

The association of OSA with increased mortality has been clearly documented since 1988, when patients with apnea index > 20 were observed to show clearly elevated mortality compared with those having a lower apnea frequency. This was particularly true in patients younger than 50 years. None of the patients treated with tracheostomy or continuous positive airway pressure (CPAP) died during the decade when they were under study (218).

With ongoing exposure to OSA, patients have been found to have increasing cardiovascular risk with elevated heart rates, increasing blood pressure variability, and blunted heart rate variability (219). Hypertension is associated with OSA, in part relating to vasoconstriction responsive to elevated endothelin function and decreased levels of nitric oxide (220, 221). Oxidative stress and inflammatory processes may be proponents of the cardiovascular risk (175). There is a clear relationship between OSA and the development of hypertension (222). This may be the predominant influence on the development of congestive heart failure (CHF), which has long been recognized as a risk of chronic, untreated OSA. At least 10% of patients with CHF have OSA (223) and these patients may report lesser degrees of daytime sleepiness than those without CHF (224). Many patients with OSA have atrial fibrillation but it is not yet clear if this is of etiological relevance in either direction (225). Additionally, insulin resistance, diabetes, and increased leptin levels occur more in patients with OSA than in weight adjusted comparison subjects (226, 227).

It appears that the intermittent hypoxemia associated with repetitive apnea or hypopnea events is likely a major pathophysiological contributor to oxidative stress and the development of the complications of OSA most responsible for its morbidity and mortality risks. These include consequences associated with OSA such as obesity, diabetes type 2, metabolic syndrome, as well as cardiovascular and neuropsychological disorders (228).

37.5.8. Differential Diagnosis

Other causes of excessive daytime sleepiness such as narcolepsy, idiopathic hypersomnia, insufficient nocturnal sleep, and sleepiness related to medical and/or pharmacological factors must be considered. Other sleep-related breathing disorders are the central sleep apnea syndromes such as appear in some neurological disorders, Cheyne-Stokes respiration of CHF, high altitude, and exposure to opioids. These all may certainly coexist with OSA in many cases.

37.5.9. Treatment

Prior to the introduction of continuous positive airway pressure (CPAP), the primary therapy for severe OSA was tracheostomy. This produces immediate benefit due to bypass of the upper (pharyngeal) airway space, allowing unimpeded ventilation. Weight loss for overweight patients remains a strong component of therapy though success is difficult to achieve. Hence, bariatric surgery and other means of weight loss have been utilized with definite improvement (211, 229). The standard treatment for OSA is CPAP, developed in the 1970's to provide a pneumatic splint for the upper airway by administration of positive pressure through a nasal or oronasal mask interface (230). Pressure is initially determined by titration during PSG though a number of automated CPAP machines are available to adjust pressure based on machine response to air flow obstruction. The advantage of PSG is the direct observation by technologists who can control mask leak, observe the effects of body position and sleep stage, and clearly distinguish periods of sleep from those of wakefulness. CPAP use distinctly improves daytime sleepiness (231, 232). Though long-term outcomes are not clearly known, CPAP in the short term has been shown to improve endothelin levels and blood pressure (221, 224, 233, 234) nitric oxide levels (235), glucose intolerance (236, 237), leptin levels and central obesity (238), left ventricular ejection fraction (224), urinary catecholamine levels (239), and the recurrence rate of atrial fibrillation (240). Unfortunately, adherence to nightly use of CPAP remains much less than desired for many reasons, including claustrophobia, interface failures, and other determinants of motivation (241). Some patients can utilize desensitization techniques but others may ultimately be unable to benefit from CPAP (242).

Other PAP treatments include auto-titrating PAP, which change the treatment pressure based on feedback from various patient measures such as airflow and airway resistance. These devices may have a role in initiating treatment in patients who are diagnosed with OSA using portable sleep studies, in which CPAP titration is not performed in a sleep laboratory. In addition, auto-titrating PAP offers the possibility of changes in pressure over time, such as with position changes during the night or over longer term for adjustment in response to weight change (243).

Some patients develop CPAP emergent central apneas (Complex Sleep Apnea Syndrome CompSAS). Patients are said to have CompSAS when they have polysomnographic finding diagnostic of OSA, but during stabilization of the upper airway using CPAP or PAP, they exhibit new central apneas sufficient to satisfy the diagnosis of CSA (244). Hence, PAP may appear to magnify or precipitate the central apneas. This occurs in patients predisposed by the inherent sensitivity of their chemoreceptors or other factors such as CHF or opioid drug use. Some studies suggest that up to 20%–50% of CompSAS patients get acclimatized to CPAP, with normalization of sleep disordered breathing over several months. Some may need more elaborate positive pressure support to regularize respiratory rate (245).

When clear anatomical obstruction such as adenotonsillar hypertrophy or mass lesion is present, surgery is indicated. In patients unable to use CPAP, various surgical procedures have been utilized. Uvulopalatopharyngoplasty alone is frequently ineffective (246). When done in combination with establishment of forward tension on the base of the tongue, efficacy can be increased. In cases of severe maxillo-facial abnormality, advancement of both maxilla and mandible can be performed (247–249). Oral appliances that hold the mandible in an advanced position during the night can be effective (214). Patients demonstrating OSA exclusively during sleep in the supine position may benefit by training to sleep only on either side. There is as yet, no pharmacological therapy for OSA. Patients experiencing residual sleepiness following treatment of OSA have been shown to benefit from modafinil (250).

37.6. Hypersomnia

37.6.1. Definition

Current psychiatric diagnostic formulation distinguishes two basic categories of disorders of excessive sleepiness, hypersomnolence disorder, and narcolepsy. The former represents excessive sleepiness despite reasonably adequate nocturnal sleep duration. The latter includes recurring periods of intense sleepiness in individuals having cataplexy (spells of diminished muscle tone), or deficient levels of CSF hypocretin, or overnight, or polysomnographic features of sleep-onset REM periods.

The ICSD-2 distinguishes hypersomnias of central origin from other disorders causing excessive daytime sleepiness such as circadian rhythm sleep disorders, sleep-related breathing disorders, or other causes of disturbed nocturnal sleep. In this nosology, primary hypersomnia of DSM-5 corresponds most directly with the category known for many years as idiopathic hypersomnia. The variant of this, which has been previously designated as the polysymptomatic form is now known as idiopathic hypersomnia with long sleep time. It is defined as (A) a complaint of excessive daytime sleepiness occurring almost daily for at least 3 months. History, sleep logs, or actigraphy reveal (B) prolonged (more than 10 hours) nocturnal sleep time and difficulty awakening fully from any diurnal or nocturnal sleep, and (C) no alternative causes are revealed by overnight PSG which demonstrates (D) short sleep latency and >10 hours of total sleep time. If MSLT is performed, (E) it reveals mean sleep latency <8 minutes and fewer than 2 sleep onset REM periods (SOREMPS) on four or five nap opportunities. In contrast, idiopathic hypersomnia without long sleep time is defined by (A) the same complaint of excessive daytime sleepiness, (B) habitual sleep of >6 but <10 hours, (C) with exclusion of other sleep disorders by PSG which (D) demonstrates a normal overnight sleep duration >6 and <10 hours. MSLT must be performed and reveals (E) mean sleep latency <8 minutes and fewer than 2 SOREMPS (17).

Narcolepsy is divided into cases with and without cataplexy. In either case, there is a complaint (A) of excessive daytime sleepiness almost daily for at least 3 months. In the former case, there is (B) a definite history of cataplexy and (C) the diagnosis is, whenever possible, confirmed with nocturnal PSG and MSLT with mean sleep latency <8 minutes and SOREMPS recorded on at least 2 naps. Alternatively, a CSF hypocretin level ≤ 110 pg/ml or 1/3 of mean normal control values is diagnostic. In narcolepsy without cataplexy, there is (A) the same complaint of daytime sleepiness, but (B) cataplexy is absent, doubtful, or atypical. (C) PSG and the same MSLT findings are required. In both cases, (D) the sleepiness cannot be better explained by another sleep, medical, neurological, or psychiatric disorder nor any substance or medication (17).

37.6.2. Epidemiology

Excessive daytime sleepiness as a non-specific symptom may be reported by as many as 15% of the general population but varies between studies and countries. Prevalence of combined varieties of specifically central nervous system-mediated sleepiness is more difficult to establish and may range from as high as 2–3% to less than 1% of the population (251). In a large scale telephonic inventory, as many as 1.6% of a European and UK sample nap at least twice a day. Cataplexy appeared to be over-

estimated at 1.6% of the same population because most subjects who reported it did not endorse sleepiness. Diagnosable narcolepsy appeared to have a prevalence of 0.047% (252). Two other studies of narcolepsy in Italy and Finland have described prevalence between 0.026–0.04% (252). In Israel, prevalence as low as 1:500,000–1:660,000 has been reported (253), whereas in Japan, it has been as high as 0.16% (254). A retrospective study of narcolepsy in Olmstead County, Minnesota reports a prevalence of 0.056% (0.036% for narcolepsy with cataplexy, and 0.021% those without) (255). Prevalence of idiopathic hypersomnia appears to be about 10% of the rate for narcolepsy (256).

37.6.3. Clinical Picture

The central feature of disorders of excessive sleepiness is the tendency to fall asleep during the wake phase of an individual's day or to experience prolonged nocturnal sleep and/or daytime napping. This is distinct from a perception of fatigue but lacking the tendency to fall asleep even for a few minutes. Symptomatic sleepiness is based upon self-report but corroborative history from family or friends is valuable. It usually corresponds with a score of 12 or greater on the Epworth Sleepiness Scale, but this is not definitive (180, 181). Idiopathic hypersomnia patients never develop cataplexy or nocturnal sleep disturbance (256). Naps, unlike for narcoleptics, are unrefreshing and may be prolonged (257). For some patients, not only is arousal from sleep difficult, but also it can be accompanied by irritability, confusion, and motor discoordination that have been called "sleep drunkenness" (258).

The classical primary hypersomnia condition, narcolepsy, was first described in France by Gélineau in 1880. He described two core symptoms of "narcolepsie" or sleep attacks and periods of "astasie" or sudden loss of muscle tone now known as cataplexy (259). Cataplexy is a relatively brief period of diminished or lost motor tone typically precipitated by emotion, most frequently laughter (260). It can cause loss of upright posture when seated or standing but may be as mild as drooping facial muscles or slurred speech. Weakness is bilateral and there are absent deep tendon reflexes during spells (261). These core symptoms become a tetrad in later literature with subsequent addition of sleep paralysis (SP), or waking from sleep with persisting loss of muscle tone, and hypnagogic or hypnopompic hallucinations (HH) (262). These so-called accessory symptoms represent components of normal REM sleep (muscle atonia and dream imagery), which become dissociated from the parent physiological state to appear abnormally during wakefulness (cataplexy) and transitions into or out of sleep (HH, SP).

More recently, spells of automatic behavior (unrecalled, often nonsensical or "absent minded") have been described (257). Also mentioned are disturbed continuity of nocturnal sleep, less problematic in young patients, increases with advancing age. Unwanted periods of sleep tend to occur after a few hours of wakefulness and may last for minutes up to an hour. Nocturnal sleep and daytime naps are generally experienced as refreshing (263).

Narcoleptic symptoms can be misinterpreted as psychiatric, such as cataplectic gait disturbance diagnosed as psychogenic (264), and hypnagogic hallucinations as schizophrenic (265, 266) or psychotic features of bipolar disorder (267).

37.6.4. Case History

A 30-year-old single man began falling asleep during classes in high school. He was regarded as a "weird kid" who would fall asleep even in the company of friends listening to music or watching sporting events. He graduated from college after 6 years of study but found it difficult to remain awake during classes. He began carrying large containers of coffee to lecture halls and the library. When he was 19 years old, he experienced the onset of unusual spells of weakness and slurred speech when caused to laugh by his friends. They knew that he could be made to appear drunk without having consumed any alcohol. He began socializing less because his friends would provoke him with jokes and gags in order to precipitate this. More and more, he struggled to remain sedate and aloof from others, for fear of "losing control" and being forced to sit slumped in a chair, unable to move either arm, or stand without support. His parents considered him to be "odd but sensitive" and tried to protect him. They encouraged his social withdrawal in spite of the fact that all who knew him regarded him as sensible and kind. He has intense interests in music, politics, and sports. During a visit to his physician for evaluation of earache, he falls asleep during the examination, and is then referred to a sleep disorders center. Overnight PSG is unremarkable other than REM latency of 45 minutes. On MSLT, mean sleep onset latency is 2.7 minutes with clear REM sleep during three of four naps. After partial improvement of wake maintenance on modafinil 400 mg daily, this is changed to methylphenidate 40 mg daily with remarkable benefit. Cataplexy finally remits after the addition of imipramine, titrated to 25 mg twice daily.

37.6.5. Laboratory Findings

PSG findings that confirm the diagnosis of narcolepsy include adequate nocturnal sleep hours, possible early onset of the first REM period, and no identifiable cause of daytime sleepiness. MSLT is begun 2 hours after final morning awakening from the

PSG study. With similar physiological monitoring, patients are observed during four or five 20-minute nap opportunities. The time between the beginning of each nap to onset of the first stage of scoreable sleep is determined. If sleep occurs, it is observed for 15 minutes for scoring of sleep stages before awakening the patient. In the case of narcolepsy, hypersomnia is evidenced by mean sleep latency ≤ 8 minutes as well as the occurrence of REM sleep (SOREMPS) during at least 2 naps (183).

A variation of the MSLT protocol has been developed to monitor the capacity of individuals to remain awake, but is not used for diagnosis. The maintenance of wakefulness test (MWT) is conducted with the patient instructed to remain immobile while seated on a bed in a darkened, quiet room. He or she is told to remain awake during four sessions of 40 minutes duration. The onset of any sleep is scored as in the MSLT, but no sleep is allowed to accumulate. If no sleep is recorded, the test is consistent with the strongest objective indication of intact capacity to remain awake while a mean sleep latency of <8 minutes indicates abnormal sleepiness. Scored for the first epoch of any sleep stage, mean latencies between 8 and 40 minutes are of uncertain clinical significance (268).

The use of a wrist-worn activity monitor coupled with a subjective sleep-wake diary can help evaluate the possibility of chronically insufficient sleep (269). Changes of pupillary diameter and light response have been used to assess non-specific sleepiness, which is associated with miosis (270, 271).

Narcoleptic patients with cataplexy have been found to have high (85–90%) presence of a human leukocyte antigen (HLA) allele, DQB1*0602, present in only about 25% of the general population. About 40% of narcoleptics without cataplexy carry this allele (272, 273). More recently, determination of hypocretin (orexin) concentration in cerebrospinal fluid has been helpful in distinguishing narcolepsy with cataplexy, for which an undetectable level is a highly specific finding. This specificity is limited to classical narcolepsy with cataplexy in the presence of the HLA DQB1*0602 allele. Detectable or normal CSF hypocretin levels are found in cases of narcolepsy without cataplexy and those with cataplexy but without the HLA marker (274, 275).

37.6.6. Clinical Course

Idiopathic hypersomnia probably presents before 30 years of age. Sleepiness is continuous during the day but with less intense "sleep attacks" than in narcoleptics (256). Spontaneous remission is unlikely. The onset of narcoleptic symptoms typically occurs around the time of puberty with peak incidence rate in the second decade (275). Many fewer cases develop in the 4th and 5th decades. The correct diagnosis is frequently delayed by up to 10 years (276). Cataplexy may occur near the time of onset of sleepiness, but can develop significantly later in many cases. Hypnagogic and hypnopompic hallucinations as well as sleep paralysis are much less specific for narcolepsy than is cataplexy and occur frequently in normals (263). As time passes, symptoms of sleepiness can have significant negative effects on mood and health-related quality of life (277, 278). With aging, there is an increasing tendency to have more fragmented nocturnal sleep and some patients have developed REM sleep behavior disorder, also based upon dysregulated REM sleep physiology (279, 280).

37.6.7. Differential Diagnosis

Recurrent hypersomnia, especially the Kleine-Levin syndrome, is rare (about 200 cases reported), more common in males, with adolescent onset, and typically remitting after a few years. Spells of hypersomnia last many days with very long bouts of sleep punctuated by brief and abnormal wakeful periods that typically include hyperphagia and hypersexuality (17, 281). Hypersomnia conditions must be distinguished from behaviorally induced insufficient sleep syndrome and sleepiness due to substances, medications, and medical disorders.

Though mood disorders are often associated with fatigue, lethargy, and/or psychomotor retardation, they are not typically associated with actual hypersomnia unless mediated by medication (282). If hypersomnia is difficult to distinguish from fatigue with depression, PSG and MSLT documentation are required (283). Other sleep disorders such as OSA and restless legs syndrome with periodic limb movement disorder may be associated with hypersomnia. This is important, because shift work (for males), sleep restriction, antidepressant use, and possibly OSA, can also be associated with SOREMPS not necessarily due to narcolepsy (284–287). Circadian rhythm sleep disorders are associated with sleep propensity at unusual times such as in the early evening with the advanced sleep phase type or in the morning with delayed sleep phase type. Similarly jet lag and shift work sleep disorders can include periods of heightened sleepiness.

Secondary, or symptomatic narcolepsy caused by other brain disorders has been described in association with diencephalic and brainstem neoplasm or infarction, other diencephalic lesions, pituitary-hypothalamic disease, and multiple sclerosis. Head trauma can be associated with hypersomnia, but not typically the narcolepsy syndrome (287). Secondary narcolepsy is not associated with HLA-DQB1*0602 at rates beyond those of the general population (261).

Isolated sleep paralysis, at sleep onset or offset, may occur independently of narcolepsy. It may be accompanied by hallucinatory experience but is not associated with cataplexy. It has been noted in folklore throughout history and underlies the descriptions of the medieval European incubus and Newfoundland Old Hag nocturnal assaults characterized by partial awakening often early in the sleep period with a sensation of an evil presence, muscle paralysis, a feeling of suffocation, and intense fear (288).

37.6.8. Etiology

The etiology of classical narcolepsy with cataplexy has been attributed to the loss of neurons in the lateral hypothalamus that secrete the single peptide known both as orexin and hypocretin because it has been studied with respect to feeding as well as sleep behavior. Mouse knockout preparations and canine species bred for deficient hypocretin receptors have further clarified this pathophysiological mechanism. Onset of human narcolepsy often follows some form of stress, which may influence the damage to hypocretin secreting cells. These stresses include head trauma, sudden sleep-wake habit changes, and infections. There have been some cases of narcolepsy reported following vaccination or infection with H1N1 influenza, but an etiological relationship has not been clearly established (289)[2]. The presence of HLA-DQB1-0602 in serum of narcolepsy patients suggests an autoimmune neuronal destruction, though the exact mechanism of cell loss has not yet been fully determined. Family studies have documented the incidence of narcolepsy in 1–2% of first-degree relatives of patients, a modest increase of risk, though clearly more than in the general population. Slightly more, 4–5% have isolated excessive daytime sleepiness. Monozygotic twin discordance appears in 25–35% of reported twin pairs, further suggesting environmental influence (290)

The etiology of idiopathic hypersomnia is not known (256). Like narcolepsy, some cases seem to follow a viral illness such as Guillain-Barré syndrome, hepatitis, mononucleosis, or atypical viral pneumonia (257). Some cases may have familial distribution in which HLA-Cw2 and DR11 alleles may appear (291).

37.6.9. Treatment

Treatment of any hypersomnia must emphasize good sleep hygiene and efforts to obtain sufficient nocturnal sleep. For narcolepsy, strategic naps can be helpful, followed by variable periods of increased alertness. Such naps may be unrefreshing and followed by sleep inertia in idiopathic hypersomnia.

Pharmacological treatment is essential to support maintenance of wakefulness in narcolepsy and hypersomnolent patients. Wake-promoting drugs are very helpful though they do not entirely restore normal daytime alertness. MSLT latencies approach a maximum of about 50% of normal values with modafinil and about 65–75% with dextroamphetamine, methamphetamine, and methylphenidate (292). Modafinil, widely used in Europe before introduction into the United States, acts by an unclear mechanism on hypothalamic wake promoting areas and is often considered as the initial choice for newly diagnosed patients. It likely acts selectively to inhibit dopamine uptake but has fewer peripheral effects than the traditional stimulants. Its half-life of elimination, 12–15 hours, allows for single dosing schedules, but can be divided into morning and noon administration. It is available in racemic as well as R-isomer forms, the latter generally having longer half-life of elimination and double the potency per milligram. It is also indicated for residual hypersomnia in patients treated for obstructive sleep apnea (293). The traditional stimulant drugs (amphetamine, methamphetamine, methylphenidate) act by dopamine reuptake inhibition and enhanced release to increase behavioral arousal. High doses of these agents (>120 mg methylphenidate, amphetamine, dextroamphetamine, or >100 mg methamphetamine) may be required in occasional patients but caution is then advised in view of potential psychiatric side effects such as psychosis, substance misuse, and psychiatric hospitalizations as well as tachyarrhythmias and anorexia or weight loss (294). Sodium oxybate (gamma hydroxybutyrate, or GHB) has been marketed to enhance daytime alertness as well as nocturnal sleep continuity. It was originally marketed for treatment of cataplexy. It must be taken in divided doses at bedtime and again during the night, 4 hours later (295). Because it has been a drug of considerable abuse potential, its use is very strictly regulated. It should be reserved for cases clearly not responsive to more conventional therapy. Cataplexy does not typically remit with stimulant or modafinil therapy, but responds to adjunctive REM inhibiting drugs such as tricyclic, SNRI, SSRI antidepressants as well as sodium oxybate. Venlafaxine and atomoxetine have also been reportedly effective (257, 296).

[2]Editor's note: A report in 2015 provided evidence for cross-reactivity between antibodies to vaccine-related influenza nucleoprotein and human hypocretin receptor 2 protein sequence as being the etiological factor responsible for induction of narcolepsy in the vaccinated subjects (414).

37.7. Parasomnias

37.7.1. Definition

Parasomnias are disorders marked by undesirable physical and/or experiential phenomena occurring during entry into sleep, within sleep, or during arousals from sleep. They may involve motoric and/or autonomic activation. DSM-5 distinguishes non-REM arousal disorders such as sleepwalking and sleep terrors from nightmare disorder (formerly known as dream anxiety disorder), and REM sleep behavior (1). This categorization tends to understate the richness of the various disorders representing, as a group, the unusual and frequently bizarre manifestations of sleep-wake state misalignment. When states of sleep and wake are incompletely separated, experiential, cognitive, behavioral, and autonomic components of one state overlap with those of the other and the consequence is an abnormal combination such as complex frenzied emotion and/or ambulation during incomplete wakefulness that can carry serious risk of injury to self or others. Any imaginable superimposition of sleep and wakeful behavior has or will appear in the medical literature.

The ICSD-2 cites disorders of arousal from non-REM sleep as distinct from parasomnias usually associated with REM sleep. The former include the prototype of their group: confusional arousals. These are recurrent, usually brief spells of apparent awakening from nocturnal or napping sleep with confusion. This is the "sleep drunkenness" of older literature and represents incomplete awakening that may include disorientation, blunted responsiveness to stimuli, and memory impairment. Two variants in adolescents and adults, severe morning sleep inertia, and sleep-related abnormal sexual behaviors are also recognized. Sleepwalking includes (A) ambulation during sleep, (B) persistence of sleep, altered consciousness, or impaired judgment and at least one of: 1) difficulty arousing the person, 2) confusion on awakening, 3) complete or partial amnesia, 4) routine behaviors occurring at inappropriate times, 5) inappropriate or nonsensical behaviors, or 6) dangerous or potentially dangerous behaviors. Sleep terrors are spells of (A) intense fear during sleep, usually initiated by a loud vocalization. These include (B) at least one of: 1) difficulty arousing the person, 2) confusion when awakened, 3) complete or partial amnesia, or 4) dangerous or potentially dangerous behaviors. (C) Both sleepwalking and sleep terrors are not better explained by any other sleep, medical, neurological, mental, substance use disorders, or medication use (17).

Parasomnias usually associated with REM sleep include REM sleep behavior disorder (RBD), recurrent isolated sleep paralysis, and nightmare disorder. Sleep paralysis, not limited to narcolepsy, is a transient, (A) inability to move trunk and limbs when awakening from sleep or, in some cases, at sleep onset lasting (B) seconds to a few minutes. This represents peripheral muscle atonia of REM sleep dissociated from normal REM sleep, and appearing or persisting at inappropriate times (15). Nightmare disorder designates (A) recurrent awakenings from sleep during very disturbing dream experiences that can include many diverse emotions, typically fear and anxiety, which are followed by (B) full alertness on awakening with clear recall of dream content. (C) There must also be at least one of 1) delayed return to sleep, and/or 2) spell occurrences during the latter half of the habitual sleep period (17).

The quintessential REM sleep parasomnia is RBD. Diagnostic criteria include (A) polysomnographic finding of REM sleep without atonia such as abnormal persistence of electromyographic muscle tone or excessive intermittent muscle twitching during REM sleep, and (B) at least one of 1) a history of sleep-related behavior that is potentially or actually injurious or disruptive, or 2) polysomnographic evidence of behaviors during REM sleep. There is also (C) absence of electroencephalographic epileptiform or clinical seizure activity during REM sleep (17)

37.7.2. Epidemiology

The prevalence of disorders of arousal has been estimated at 1–6.5% for sleep terrors, and 5–30% for sleepwalking in children and adolescents (297–299). It has been estimated that 2–5% of adults may experience sleepwalking (300–302). A large systematic telephonic survey of individuals aged 15 years and older in the United Kingdom documents sleep terrors in 2.2% (2.6% for ages 15–24, 1.0% for ages>65), sleepwalking episodes in 2.0% (4.9% for ages 15–24, 0.5% for ages>65), and confusional arousals in 4.2% (8.9% for ages 15–24, 1.4% for ages>65). In the same population, 2.0% of all respondents reported some violent behavior during sleep. The authors note the absence of chronically ill or institutionalized subjects in the general population sampled, ruling out estimation of the prevalence of REM sleep behavior disorder that is found predominantly in the elderly (303). In a large telephonic study in the general American population older than 18 years, lifetime prevalence of "nocturnal wandering" (spells of sleep-related behavior beyond the bed) was 29.6%. Incidence during the prior year was 3.6%. Positive family history was reported by 30.5%. There was no difference in prevalence between those with and without history of SSRI drug use, but there was an association with major depressive disorder and obsessive-compulsive disorder (304).

37.7.3. Clinical Picture

Sleepwalking is characterized by abrupt arousals from sleep with movement from the bed that can include complex, automatic behaviors such as wandering about, carrying objects from place to place without reason, rearranging furniture, eating inappropriately, urinating in closets, going out of doors, and rarely even driving an automobile (305). Eyes may be open but with glassy stare. Communication is variable, but the individual may mumble or speak nonsensically. Frenzied, aggressive behavior is possible and may involve use of weapons. The effects of suspended judgment can result in inadvertent injury or death to the sleepwalker or someone else (306, 307).

Spells of sleepwalking typically emerge during the first third of the sleep period, when non-REM sleep, particularly stage N3, predominates. They generally last for minutes to an hour, though with great variability. Sleep terrors typically begin with sudden, loud screaming accompanied by tachycardia, tachypnea, and mydriasis, with unresponsiveness to consolation. In some cases, frenzied motor behavior can ensue. Pure sleep terrors occur commonly in children, who return to sleep without difficulty and awaken unperturbed in the morning in contrast to the parents, for whom the spells are most troubling. In both disorders, patients are typically amnestic for the spells. Adults with disorders of arousal often experience mixed SW and ST associated with either fragmentary or elaborate dream imagery (308, 309).

Dream enactment, or spells of oneiric behavior of RBD tend to emerge at least 90 minutes after sleep onset and especially during the latter part of the night when REM sleep periods are of longer duration with more dense phasic eye movements. Behaviors are typically aggressive or exploratory and never appetitive (feeding, sexual). They are usually quite abrupt and brief in duration. There is very active dream content, often with preceding prodromal action-packed dreaming for months or years before sleep-related behavior begins. Behavior is clearly concordant with reported dream content, which usually involves confrontation, aggression, and violence in spite of usually calm and pleasant wakeful personalities. Behavioral features of the disorder are indistinguishable across genders, ages, and presence or absence of neurological disorder (310). Recently, a video and book containing a large number of patients' descriptions of their parasomnias, along with pertinent clinical and scientific information has been published. A documentary film on the topic has been produced (308, 309, 311).

Many interesting variations of these disorders have been reported. Overlapping non-REM and REM sleep parasomnias can co-occur in the same patient (312). Sleep-related eating disorder, now recognized as a distinct parasomnia, is most often a variant of sleepwalking and includes eating rich, often thick fluids, such as milk shakes, peanut butter, or brownies, and may involve unusual substances that would not be consumed during wakefulness. It is not associated with awareness of hunger or thirst in spite of a drive to eat described as "out of control". There is no associated purging and more than 40% of patients are overweight (313–315). Other associated risk factors for SRED include RLS, PLMD, OSA, and zolpidem use, but it is also idiopathic in many cases. Interesting is the reported association of zolpidem-related SRED and RLS (WED) in a recently published case series (316). Sleep-related sexual behavior can also occur during sleep and may be confused with wakeful, inappropriate conduct (317, 318).

Numerous other parasomnias are included within the ICSD-2, and the reader is referred there for descriptions including recurrent isolated sleep paralysis, sleep enuresis, sleep-related groaning, exploding head syndrome, and sleep-related hallucinations (17).

37.7.4. Case Histories

37.7.4.1. SW/ST

A 28-year-old man with a history of sleepwalking from ages of 5 to 10 begins to have nocturnal spells increasingly frequently during the 5 months after beginning a new job. He is required to begin his workday about 2 hours earlier than for his former employment. About 3 or more times weekly, within 2–3 hours after falling asleep, he is observed to moan or yell, and then arise to walk briskly out of the room or into a closet. These events typically last several minutes and he often pounds on the wall or floor before returning to bed and to sleep, with no recall of the experiences the following morning. He is brought to an emergency room one night after punching a bathroom window and suffering lacerations to the right hand and wrist. He recalls dreaming that some vague, darkly cloaked assailant seemed to be threatening harm, and then he awakened with a bloody hand. His fiancée later demands that he pursue psychiatric consultation, assuming that he was expressing anger during sleep rather than talking openly with his rigid supervisor at the workplace. The psychiatrist prescribes clonazepam 0.5 mg taken 20 minutes before bedtime for one month, during which the patient begins going to bed an hour earlier each night and practices a relaxing exercise of self hypnosis with imagery of peaceful sleep. He remains free of spells thereafter.

37.7.4.2. RBD

For a period of 6 months, a 77-year-old man has almost nightly spells of yelling with vigorous arm and leg movements that have caused bruises to his wife. He is a mild mannered person by day, but he curses and punches violently at assailants in the visually vivid dreams that occur predominantly in the early morning hours. For many years before these behaviors emerged, he experienced action-packed dreaming with violent content. His wife can no longer share the same bed with him, so he uses a smaller bed in an adjoining room. He is brought to his physician the day after having fallen from bed, suffering a fractured wrist during a spell. He recalls dreaming that he was chasing and beating a man who had threatened him. Mental status and neurological examinations reveal no notable findings. After subsequent referral to a sleep center, he undergoes PSG revealing bursts of muscle tone and extremity movement during apparent REM sleep. He begins sleeping peacefully with no motor activation following prescription of clonazepam, initially 0.25, then 0.5 mg taken 20 minutes before bedtime. He is then sent to a neurologist for long-term follow-up after a frank discussion of the possibility for future development of neurodegenerative illness.

37.7.5. Laboratory Findings

On PSG, there are few diagnostic markers of disorders of arousal in the absence of a spell. Bursts of slow EEG waveforms known as hypersynchronous delta activity are possible indicators of a drive to enhance depth of sleep but are not specific to these disorders (319). Actual episodes of sleepwalking or sleep terrors are often not observed during PSG. When they occur, they appear as abrupt arousals from non-REM sleep, typically but not exclusively from stage N3. With sleep terrors, there may be impressive tachycardia and tachypnea. Muscle activity often obscures the underlying EEG, which can demonstrate diffuse rhythmic delta activity, diffuse delta and theta activity intermixed with alpha and beta activity, and/or prominent alpha and beta activity. Hence, the EEG during episodes of disorders of arousal can show either the complete persistence of sleep, the admixture of sleep and wakefulness, or complete wakefulness in spite of the behavioral manifestations of a mixed state (320, 321).

Brain imaging studies are not utilized for clinical evaluation though a case report with SPECT imaging during a sleepwalking spell has demonstrated cerebral blood flow (CBF) to be increased in the anterior cerebellum (vermis) and posterior cingulate cortex when compared to quiet slow wave sleep. There are also large areas of frontal and parietal cortex decrements of CBF when compared with normal awake subjects. Sleepwalking appears to represent a concurrence of increased motor activation and decreased executive function during incomplete, disordered arousals from sleep (322) (Fig. 37.7).

In the case of RBD, there is preserved normal cycling of non-REM and REM sleep stages as well as distribution of all sleep stages. The characteristically increased electromyographic muscle tone and/or extremity movement during REM sleep is

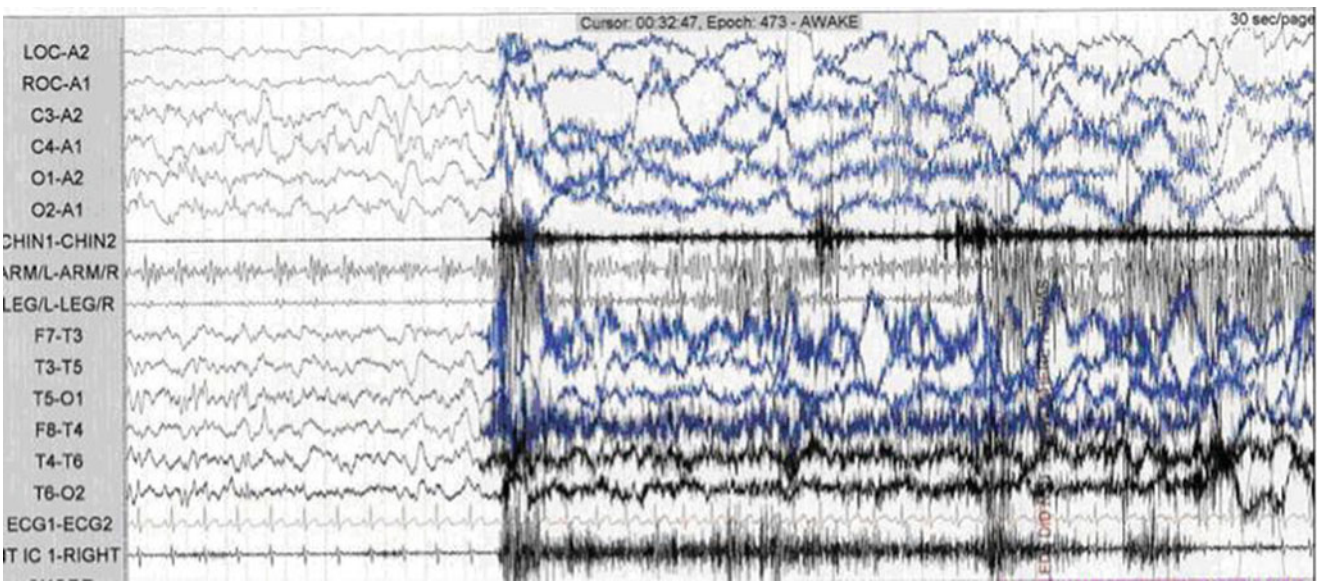


FIGURE 37.7 A 30-second epoch demonstrating an abrupt arousal from non-REM stage N3 sleep with subsequent movement and muscle artifact obscuring most of the underlying EEG in a patient with a history of sleepwalking. Note the absence of tachycardia, which would occur in classical sleep terrors.

usually based upon the interpretation of an experienced sleep specialist. A scoring system, however, has been proposed to quantify the degree of abnormal motor activity (12, 323, 324). Importantly, there may be epochs of REM sleep with normal muscle atonia in a given muscle group (e.g., under the chin) concurrent with bursts of tone or movement in another group (e.g., a limb). When an actual behavioral event is observed, it is clearly related to a period of REM sleep and the laboratory technologist can subsequently ask the patient for a description of dream content which is typically concordant with the behavior just observed.

Neuropsychological testing, though not indicated for diagnosis, has revealed dysfunctional visuospatial constructional ability and altered visuospatial learning in early, apparently idiopathic RBD. This may be consistent with the possibility of underlying neurodegenerative disorder (325).

37.7.6. Clinical Course

Commonly beginning in childhood, sleepwalking peaks between 11–12 years of age. Sleepwalking and sleep terrors generally subside in later childhood and adolescence but may continue into, and rarely arise during, adulthood. RBD, on the other hand, usually presents in older adults, typically men. Idiopathic RBD in many cases is an early herald of neurodegenerative disorders associated with deposits of alpha-synuclein, a protein component of intracellular inclusion bodies in brains of patients suffering Parkinsons disease, dementia with Lewy bodies, and multiple system atrophy (MSA) (326). In an early series of cases followed over more than a decade, 38% (11/29) of cases initially diagnosed as idiopathic RBD evolved into a parkinsonian disorder after a mean of nearly 4 years after diagnosis of RBD and nearly 13 years after its onset (327). With time, this same cohort yielded a total of 65.4% (17/26) developing a parkinsonian disorder or dementia without Parkinsonism (in 1 case) over an average of 13.3 years following onset of RBD (328). More recent data, as the follow-up interval increases, indicate that RBD association with Parkinsons Disease in males approaches 82%. Similarly, associations with Lewy Body Dementia have approached 82%, and Multi System Atrophy, 64% (329, 330). In view of this and neuropsychological deficits of impaired visuospatial constructional performance, visuospatial learning, verbal memory, executive problem solving, and/or verbal associative fluency resembling those of dementia with Lewy bodies in a number of idiopathic RBD cases, some authors have suggested that idiopathic RBD might rather be designated cryptogenic RBD (331).

Violent parasomnias, disorders of arousal as well as RBD, can be associated with very complex behavior and serious risk of injury. Cases of sleepwalking/sleep terrors have been documented to include long distance driving (305) and rarely even homicide (306, 307). Spells of RBD are typically abrupt, usually of brief duration, and can yield injuries in as many as 79–96% of patients who enact dreams of violent content resulting in fractures and lacerations. This also causes injury to bed partners in a number of reported cases. Both disorders of arousal and RBD tend to occur independent of any psychiatric disorder (307, 332), though the former are typically more likely to occur during periods of stress and the latter have been reported in a few cases as sequelae of severe psychological stress (332, 334). A large epidemiological survey has found violent sleep-related behavior to be more frequently acknowledged in persons with DSM-IV anxiety and mood disorders or psychotic symptoms though no etiological relationship has been clearly established with psychiatric illness (303). In another report by the same author, DSM-IV mood disorders were present in 25.8% of those reporting confusional arousals, 30.4% with sleep terrors, and 14.6% with sleepwalking. Anxiety disorders were present in 18.9% with confusional arousals, 34.2% with sleep terrors, and 12.7% with sleepwalking (335). For comparison, lifetime prevalence for major depression is 10–25% for women and 5–12% for men. Anxiety disorders have 1–5% lifetime prevalence (1).

37.7.7. Differential Diagnosis

Sleep-related seizure disorders can present as any imaginable behavioral and/or autonomic events (336–342). These have included obvious nocturnal seizures (332–338), episodic nocturnal wandering (343, 344), and hypnogenic paroxysmal dystonia (a frontal lobe seizure disorder) (345, 346). Disorders of arousal and "pseudo-RBD" can be precipitated by sleep fragmentation due to such disorders as OSA (347–351), and rhythmic movement disorders (352, 353). It is important to note that anything capable of precipitating an arousal from sleep can precipitate a disordered arousal.

Of interest to psychiatrists is nocturnal psychogenic dissociative disorder, which can resemble other parasomnias, but emerges clinically after the individual undergoes a transition from sleep to electroencephalographically determined wakefulness while appearing to remain behaviorally asleep. Most typically, these patients have DSM-IV diagnoses of daytime dissociative disorders to include borderline personality disorder. In these cases, apparently sleep-related behaviors may be self-injurious and dream-like mentation can recall past trauma. Interestingly, benzodiazepine drugs that are effective in disorders of arousals and RBD may aggravate dissociative spells (354).

Panic disorder may include nocturnal attacks that arise abruptly, most commonly during deepening non-REM sleep. Full awakening and prolonged return to sleep typically follows spells in contrast to the lack of full consciousness and prompt resumption of sleep with sleep terrors (355). Malingering remains a possibility to be kept in mind (356). Nightmares are awakenings from REM sleep with intensely discomforting dream mentation involving negative emotion of any nature. Spells are brief, and yield to full awakening without confusion or oneiric behavior. They occur commonly but not exclusively following trauma and may also occur as side effects of antidepressants, antihypertensives, dopamine receptor agonists, antihistamines, and withdrawal of REM sleep inhibiting drugs leading to REM sleep rebound (17).

37.7.8. Etiology

The neural basis for disorders of arousal has not been elucidated but must reside in the dysregulation of transitions from sleep to wakefulness. Prior sleep deprivation, causing increased physiological sleep propensity, seems to increase the likelihood of disordered arousal in predisposed individuals. It may even be used to facilitate induction of spells during PSG (357). Similarly, alcohol and sedating drugs also slow this transition. Sleepwalking and sleep terrors have been associated with olanzapine (358), lithium, and other neuroleptics, often in combination (359). Sleep-related eating has been associated with zolpidem (360), olanzapine (91), and risperidone (90). During the state of being asleep, like in the setting of some forms of epilepsy there are diminished cortical and subcortical influences on motor activation, leaving lower brainstem and spinal cord locomotion generators unimpeded and without executive controls (361).

REM sleep behavior disorder is the result of impaired muscle atonia, coupled with the liberation of typically aggressive and violent dream enactment during REM sleep. The animal model of RBD, based upon experimentally induced pontine lesions in cats, has been known since 1965 (362). Most human RBD, however, is not clearly associated with such distinct anatomical lesions. The pathophysiology of the disorder must involve both disruptions of peripheral muscle atonia and the suppression of locomotor activity that are normal components of REM sleep (363). Because of the eventual development of Parkinsons disease, dementia, and MSA in high numbers of patients with initially idiopathic RBD (52%, 60%, and 36%, respectively in one study), and the decreased striatal dopamine transporter protein shown in SPECT and PET scan studies, the etiology of RBD seems to be that of the neurodegenerative disorders. Therefore, as noted above, RBD appears to be a herald symptom (364–366). Numerous other neurodegenerative disorders may also be associated with RBD (367). It can often be attributed to REM suppressing drug use as well as withdrawal, to include tricyclic antidepressants, monoamine oxidase inhibitors, cholinergic drugs such as biperiden, selective serotonin reuptake inhibitors, mirtazapine (reported in patients with parkinsons disease), excessive caffeine use and selegiline treatment of Parkinsons Disease (310, 368–372). In a recent report of "idiopathic" RBD associated with antidepressant drugs, findings of olfactory and color vision impairment, mild cognitive disturbance, and other markers of neurodegeneration occurred to greater extent than in normal control subjects. This raises the possibility that the medications may unmask underlying RBD rather than simply cause an iatrogenic form of it (413). Narcolepsy, itself a disorder of physiological organization of REM sleep, has been associated with RBD (373). Because of the prognostic implications of a diagnosis of RBD, careful polysomnographic confirmation is important. As noted above, dream-enactment behavior can be released in the case of obstructive sleep apnea and remit with treatment of the sleep-related breathing disorder and therefore not represent actual RBD (374).

37.7.9. Treatment

Sleepwalking and sleep terrors are often benign and self-limiting, especially in children, and may require no treatment beyond reassurance and attention to sleep hygiene. Attention should be paid to safety features of the sleep environment such as placement of dangerous obstacles, accessible windows and stairways, and other dangers. If falls from bed are possible, consider placing the mattress on the floor. Instruction in self-hypnosis or relaxation-mental imagery exercises has been reported to benefit children and adults with disorders of arousal (375–378). When there is risk of injury or serious disruption to household life, pharmacotherapy should be considered. BZ's have traditionally been reported as effective, as have TCA's (379).

Conversely, a more recent report claims that clonazepam failed to demonstrate sustained efficacy in 5 SW patients. This investigation carefully excluded even subtle sleep disordered breathing. After one year all patients treated with clonazepam dropped out of the study and reported a persistence of SW (380).

Distinct from BZD and BZRA drugs, a number of antidepressants have been reported to treat NREM parasomnias, most commonly ST. One report described two patients with a history of combined ST and SW, both of whom failed diazepam therapy but responded well to imipramine (a tricyclic antidepressant) (381). The selective serotonin reuptake inhibitor (SSRI) paroxetine appears to be particularly effective in the treatment of ST. In one report 6 patients had a significant reduction if not outright

elimination of ST events. The authors suggested that SSRI's might be uniquely effective for ST through serotonin effects on terror centers in the midbrain periaqueductal grey matter (382). In contrast to these successful ST cases, a more recent series of SW patients describes 8 patients who were treated with various serotonergic agents and/or benzodiazepine. After one-year follow-up, all 8 patients described a persistence of SW (75). Further, there has been reports of paroxetine and sertraline allegedly inducing SW (383, 384).

Sleep-related eating disorder tends not to respond to benzodiazepine monotherapy, as does SW/ST. Various combinations of levodopa, opioid, bupropion, trazodone, and benzodiazepine have been reportedly helpful (313, 385). More recently, topiramate has become the treatment of choice (386, 387). In most published cases of automatic sexual behavior during sleep, or sexsomnia, clonazepam has been found to be very effective (317, 318).

Over 90% of RBD responds to clonazepam 0.5–2.0 mg at bedtime and 12 year follow-up has indicated no significant trend toward tolerance or untoward effects, though patients must be cautioned about possible morning hangover sedation (388, 389). In the 10% of cases not responsive or fully remitted with clonazepam, melatonin 3–12 mg at bedtime has become a second line agent and may be considered as initial therapy for frail or cognitively impaired individuals for whom benzodiazepine is deemed contraindicated (390–392). The mechanism of this treatment is poorly understood, but may relate to improvement in some circadian synchrony that is defective in RBD (363). Donepezil (393), pramipexole (394, 395), levodopa, carbamazepine, triazolam, clozapine, and quetiapine have been reportedly effective (310, 363, 396). Generally, however, despite the strong association of RBD and Parkinsonism, dopamine agonist therapy is not highly effective in contrast to the impressive benefit of clonazepam. Every patient with REM sleep behavior disorder must have thorough neurological assessment and should be informed of the association of RBD with neurodegenerative disorders. Regular, long term follow-up is essential.

Nightmares have been reported to benefit from dream rehearsal therapy, a technique of cognitive restructuring by rehearsing a desired, modified dream scenario during quiet wakefulness prior to retiring to bed for the night (397, 398). Pharmacotherapy with cyproheptadine has been reportedly beneficial (399–402), though one group has reported it to be ineffective (403). Prazosin (404–410), guanfacine (411), and clonidine (412) have also been reportedly helpful.

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Neuromodulation in Psychiatry

Mayur Sharma, M.D., M.Ch., Zion Zibly, M.D., Milind Deogaonkar, M.D., M.Ch., and Ali Rezai, M.D.

Abstract The success of deep brain stimulation (DBS) surgery for movement disorders over the past 20 years with over 100,000 patient implants has revived the interest in neurosurgical treatment of refractory psychiatric disorders. The introduction of stereotaxis in the second half of the twentieth century aided with the technological evolutions enabled neurosurgeons to interrupt the white matter tracts while minimizing the cortical damage and thereby the side effects associated with leucotomies/lobotomies. Moreover, the integration of functional imaging, microelectrode recordings and computer based data with stereotaxis made it a robust technique to target the subcortical structures more precisely. With better understanding of the pathophysiology and neural circuits involved in these disorders, it may be possible to delineate the anatomical "target" or "targets" for neuromodulation. The role of cortico-striato-thalamo-cortical (CSTC) loops in the pathophysiology of these psychiatric disorders is well established. Preliminary results suggested the efficacy of this treatment modality in the management of refractory psychiatric disorders such as OCD and MDD and neurostimulation therapy may be an option in the management of these disorders. There are several advantages of neurostimulation therapy over ablation therapy such as reversibility and adjustability according to the patient's symptoms and disease progression and the ability to switch the stimulation without patient's awareness, thereby providing an opportunity for blinding in crossover research studies. The opportunity for surgical intervention is of importance given the large prevalence and the socioeconomic impact of psychiatric disorders, the presence of many refractory and disabled patients, improved understanding of the neural circuitry underlying these conditions, and increasing safety, precision, and technological innovations in the neurosurgical interventions. This chapter focuses on neurosurgery for severe and treatment-refractory psychiatric disorders including history of psychosurgery, ethical considerations, current concepts, and future goals.

Keywords Neuromodulation · Deep brain stimulation · Obsessive-compulsive disorder · Major depression · Psychosurgery · Cortico-striato-thalamo-cortical loops

M. Sharma, M.D., M.Ch.
Fellow, Center of Neuromodulation, Wexner Medical Center, The Ohio State University, Columbus, OH, USA
e-mail: Mayur.Sharma@osumc.edu

Z. Zibly, M.D.
Fellow, Center of Neuromodulation, Wexner Medical Center, The Ohio State University, Columbus, OH, USA
e-mail: Zzibly@yahoo.com

M. Deogaonkar, M.D., M.Ch.
Associate Professor, Department of Neurosurgery, Center of Neuromodulation, Wexner Medical Center, The Ohio State University, Columbus, OH, USA
e-mail: Milind.Deogaonkar@osumc.edu

A. Rezai, M.D. (✉)
Professor and Stanley D. and Joan H. Ross Chair in Neuromodulation, Director, Neuroscience Program and Center for Neuromodulation, Wexner Medical Center, The Ohio State University, Columbus, OH, USA
e-mail: Ali.Rezai@osumc.edu

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38.1. Introduction

Psychiatric and Neurobehavioral disorders constitute a significant burden to the health-care system accounting for 50% of the top ten causes of disability worldwide (1). Major depression is the leading cause of disability and an estimated 15% of adults in the USA experience an episode of major depressive disorder in their lifetime (2). Moreover, treatment resistant depression is likely to affect more than one-third of the depressed patients (3). Other disorders such as alcoholism, bipolar disorders, schizophrenia, and obsessive-compulsive disorders constitute the rest of the top ten causes of disability (1). The quest to treat psychiatric disorders and modify human behavior using neurosurgical interventions can be dated back to the origin of this specialty. However, due to the lack of understanding of the pathophysiology of the disease states and their treatments, limited understanding of the targets in the brain, poor surgical safety profile, lack of standardized studies, variable outcome and reporting, and advent of effective medications, the surgical interventions were significantly reduced. Over the past decade, technological advances have not only improved our understanding of the human brain but also led to the refinement and resurgence of psychiatric neurosurgery. The introduction of stereotaxis and success of novel neurosurgical techniques such as Deep brain stimulation (DBS) for movement disorders has renewed interest in neurosurgical treatment for refractory psychiatric disorders. Given the enormous prevalence and the socioeconomic impact of psychiatric disorders along with the increasing safety and technological innovations in the neurosurgical interventions, this field is likely to gain importance in the near future. This chapter focuses on neurosurgery for severe and treatment-refractory psychiatric disorders.

38.2. History of Psychosurgery

The history of surgical interventions for psychiatric illnesses can be dated back to the origin of the mankind. The art of "Trepanation" likely for the treatment of psychiatric illnesses can be demonstrated in the skull obtained from the Neolithic burial site in France (4). In the Renaissance era, the famous Dutch painting "The Cure of Folly or The Extraction of the Stone of Madness" depicts an example of the surgical intervention to cure "madness" in that era (5).

In 1891, G. Burckhardt first published his experience with topectomies on six patients with severe psychiatric illnesses (6). However, it was not until the mid-20th century, when psychosurgery was popularized following the successful introduction of frontal lobotomy/leucotomy. These ablative techniques were introduced based on the primate research model by Fulton and Jacobsen and were subsequently performed in humans for psychiatric disorders by Moniz and Lima in 1935, for which Moniz was awarded the Nobel Prize in Physiology and medicine in 1949 (1, 7). Following the introduction of this technique by Freeman and Watts in USA, more than 20,000 transorbital frontal lobotomies were performed by 1951 (8). The widespread application of this crude surgical technique in the absence of adequately controlled trials and tools for psychiatric evaluation, often led to the devastating outcomes. The negative impact of these surgical outcomes coupled with the advent of chlorpromazine, an effective phenothiazine derivative antipsychotic, led to the rapid fall of psychosurgery. Despite this, there remained a large number of patients with refractory psychiatric illnesses and potential for improvement with psychiatric surgery. William Scoville introduced the concept of minimalism and the cortical undercutting approach in 1948 and steered the concept of psychosurgery versus what had been popularized by Freeman (9). The introduction of stereotaxis in the second half of the 20th century aided with the technological evolutions revived the interest in psychosurgery by enabling neurosurgeons to interrupt the white matter tracts while minimizing the cortical damage and thereby the side effects associated with leucotomies/lobotomies. Spiegel and Wycis introduced the Cartesian stereotactic system in 1947 and performed the first subcortical stereotactic procedure on human brain by ablating the dorsomedial thalamus in 1949 and provided a template on which all modern psychosurgery procedures are based (1, 10). The integration of functional imaging, microelectrode recordings and computer based data with stereotaxis made it a robust technique to target the subcortical structures more precisely. Using stereotactic techniques, four neurosurgical procedures were developed for the treatment of refractory psychiatric illnesses: (1) cingulotomy, (2) capsulotomy, (3) subcaudate tractotomy, and (4) limbic leucotomy. Of these, cingulotomy, capsulotomy, and limbic leucotomy are in current use for patients with severe refractory psychiatry disorders. However, these procedures are permanent, and their effects cannot be reversed, thereby demanding the more precise placement of lesion with a slight margin of error.

Following the success of brain stimulation techniques for movement disorders in the last 20 years in over 100,000 patients, there is a growing interest in the application of this technique for the treatment of refractory psychiatric disorders as well. These techniques include deep brain stimulation (DBS), epidural/subdural surface electrode placement, vagal nerve stimulation, and transcranial magnetic stimulation (TMS) (11). Of these, vagal nerve stimulation and TMS can be considered for less severe and refractory psychiatric disorders as compared to deep brain stimulation (12, 13). DBS can be a promising treatment modality for severe and treatment-refractory psychiatric disorders as more specific anatomical targets are being elucidated.

38.3. Pathophysiology and Neurocircuits

Neuromodulation for psychiatric disorders requires an appropriate selection of the surgical targets and a detailed understanding of the basic pathophysiology associated with these disorders. However, unlike movement disorders it is difficult to elucidate the neural circuits that are involved in the development and maintenance of such psychiatric illnesses due to the paucity of adequate animal models. Moreover, the behavior patterns, associated with these psychiatric disorders are very unique to human species and results from animal models need to be cautiously extrapolated to the human patients. With better understanding of the pathophysiology and neural circuits involved in these disorders, it may be possible to delineate the anatomical "target" or "targets" for Neuromodulation and thus ameliorating the clinical symptoms. Though, our understanding of these circuits continues to evolve rapidly, the role of cortico-striato-thalamo-cortical (CSTC) loops in the pathophysiology of these psychiatric disorders is well established. These neural circuits were highlighted following the development of Parkinsonism in human abusers of 1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine (MPTP) in 1983 (14). In 1986, Alexander et al. proposed at least five parallel functionally segregated circuits linking basal ganglia and cortex via thalamus (15). Each of these circuits was identified as anatomically and functionally segregated. These circuits include "motor", "occulomotor", "dorsolateral prefrontal", "anterior cingulate", and "lateral orbitofrontal" (15). The "motor" loop centers on the putamen/caudate and receives somatotopically organized projections from the motor and somatosensory cortices. The putamen projects back to the cortex, globus pallidus, and substantia nigra. The globus pallidus and substantia nigra in turn project to the thalamus. Each of these loops has segregated basal ganglionic and cortical projections. Within each circuit there are "direct" and "indirect" pathways; the direct route has two excitatory and two inhibitory pathways whereas the indirect route has three inhibitory and one excitatory connection. Therefore, the direct pathway is a net positive feedback loop and the indirect pathway can be perceived as a net negative feedback loop (16, 17). Figure 38.1 is based on this model upon which neurosurgical interventions for Parkinson's disease have been developed; therefore, it can be speculated that a similar model can be used for the development of psychosurgery as well. As mentioned the major limitation for the development of psychosurgery is the lack of appropriate animal models, though there are some studies delineating the neural circuitry involved in the development and maintenance of depression (18, 19). However, similar studies are lacking for obsessive compulsive disorders (OCD), making it a challenging endeavor to develop surgical interventions for this disorder. Jeanmonod et al. reported a particular electrophysiological pattern of activity known as thalamocortical dysrhythmia (TCD) in their results from 11 patients with various psychiatric disorders such as MDD, OCD, BPD, anxiety, and delusional disorders (20). In TCD the thalamus is either deafferentated or hyperinhibited by an unknown mechanism resulting in hyperpolarizing of thalamic cells with low threshold spikes. This model was incongruent with the proposed model of OCD/depression which involves relative increase in the excitatory loop of the corticothalamic projections. Patients with combined OCD– depression have decreased metabolism in the caudate/thalamus/hippocampus which tends to normalize with successful treatment (11, 17). These findings indicate that multiple dysregulated activities within the CSTC loop could give rise to various psychiatric disorders. Investigators targeted bilateral centrolateral thalamus and anterior medial pallidum to address the phenomenon of thalamocortical dysrhythmia, thus isolating abnormal rhythms from specific and nonspecific thalamic systems (11). Neurosurgical interventions are currently under investigation for a variety of psychiatric disorders such as MDD, OCD, substance abuse, eating disorders, and anxiety. Of these, MDD and OCD are the most elucidated and frequently targeted for the neurosurgical interventions. These disorders may provide a template to further evaluate and study the use of neurosurgical interventions for other psychiatric disorders.

38.4. Obsessive and Compulsive Disorder (OCD)

Obsessive and compulsive disorder is a relatively common psychiatric disorder with a life time prevalence of 2–3% in the USA (21). Despite aggressive pharmacotherapy and behavior therapy, 20% of the patients with OCD have persistent symptoms leading to significant functional impairment (22, 23). CSTC circuits have been implicated to have a significant role in the pathogenesis of various psychiatric disorders including OCD in humans. This fact was reiterated by the reduction in the metabolism of caudate nucleus in patients with OCD following treatment with paroxetine (24). Therefore, obsessive/compulsive symptoms can occur with either abnormally increased activity in the orbitofrontothalamic pathways or decreased activity in the striatopallidothalamic pathways. Modulating either of these pathways can ameliorate the symptoms associated with OCD. Psychiatric diseases and movement disorders may share common neural circuits in the pathogenesis of their symptomatology. The occurrence of motor tics and OCD-like symptoms in patients with Tourette syndrome support this idea of a common neural substrate involved in producing both motor and psychiatric symptoms. Moreover, abnormality in the basal ganglia circuits has been implicated in the pathogenesis of both motor and OCD-like symptoms in Tourette's syndrome (25–28). Studies involving transcranial magnetic stimulation (TMS) demonstrated significantly decreased intracortical inhibition in both Tourette's syndrome

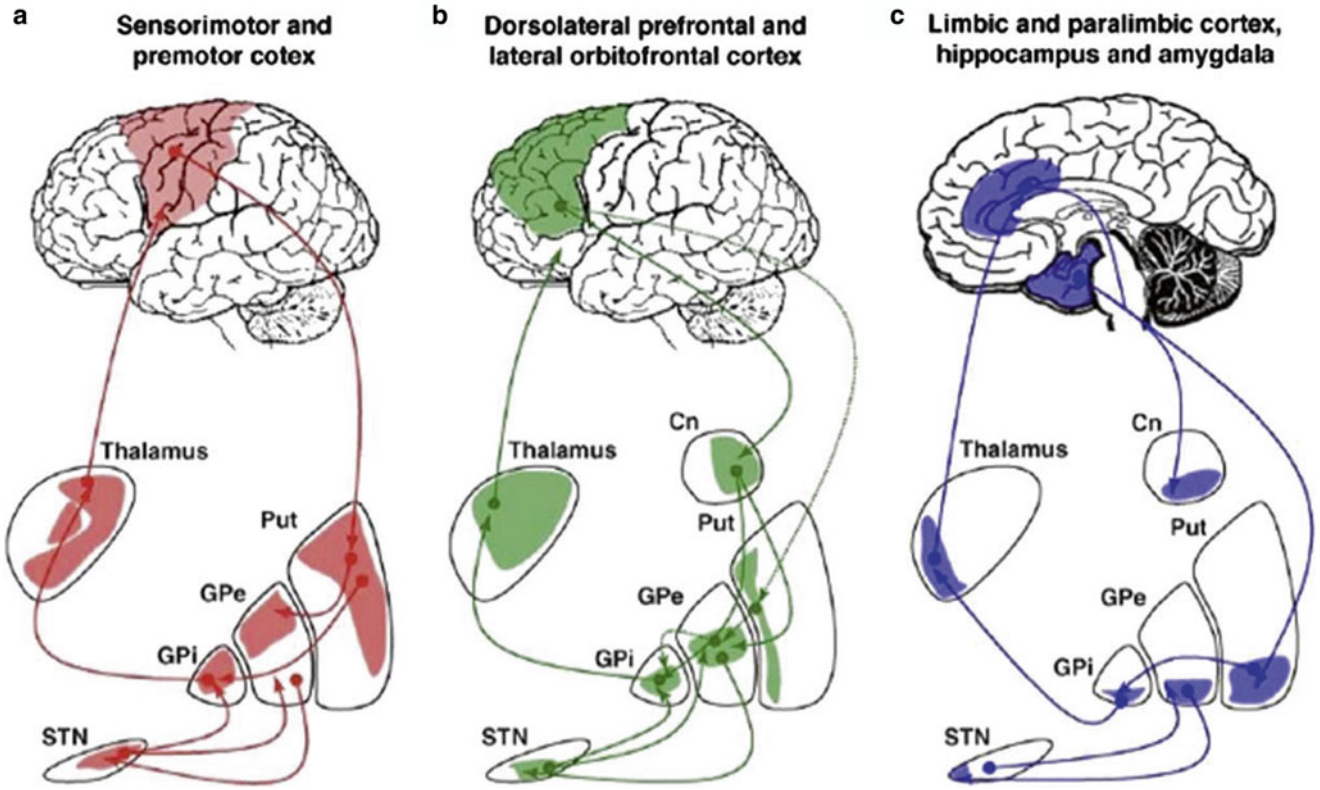

FIGURE 38.1. Schematic representation of cortico-striato-thalamocortical loops (CSTC). (**a**) *Motor circuit*: Neurons from the sensorimotor and premotor cortex project to the posterolateral portion of putamen (Put). The direct circuit connects putamen to the posterolateral region of globus pallidus pars interna (GPi) and indirect circuit connects putamen to the posterolateral region of globus pallidus pars externa (GPe), the subthalamic nucleus (STN) and the globus pallidus pars interna (GPi). GPi then projects to the ventrolateral thalamus and cortex. (**b**) *Associative circuit:* Neurons from the dorsolateral prefrontal and lateral orbitofrontal cortices projects to the striatal caudate nucleus (Cn) and anteromedial portion of the putamen. Cn and Put project to the dorsomedial portion of GPi and anteromedial portions of GPe and STN. GPe and STN then project to GPi and finally all the impulses from GPi project to the dorsolateral prefrontal and lateral orbitofrontal cortex via the anterior thalamic nuclei. (**c**) *Limbic circuit:* Neurons from the hippocampus, amygdala, paralimbic, and limbic cortex project to the ventral portion of the caudate and putamen and the nucleus accumbens (NAc). From here, the neurons then project to the limbic portion of GPe, Ventral GPi and medioventral portion of STN which in turn project to the cortex via the mediodorsal nucleus of thalamus. Reprinted from World Neurosurgery, 80, Lapidus KA, Kopell BH, Ben-Haim S, Rezai AR, Goodman WK. History of psychosurgery: a psychiatrist's perspective. S27.e1-e16, Copyright (2013) with permission from Elsevier.

and OCD, thereby strengthening the fact that these disorders are analogous disorders with a common neural substrate (11). In addition, patients with OCD and Tourette's syndrome share some clinical features with Parkinson's disease including depression (26, 29). These facts point towards a common neural substrate in the pathogenesis of both motor and psychiatric symptoms. Serotonin and dopamine dysfunction have been implicated in the pathogenesis of OCD and thereby form the basis of the utility of selective serotonin reuptake inhibitors (SSRIs) and dopaminergic atypical antipsychotics in the medical management of patients with OCD (30–32). Glutamate, gamma-amino butyric acid (GABA), Substance P, acetylcholine and endogenous peptides are other neurotransmitters implicated in the CSTC circuits and thus in the pathogenesis of OCD (16, 33, 34). Imaging studies demonstrated decrease in glutamate concentration in caudate following treatment with paroxetine in patients with OCD which corresponds to the decrease in the severity of OCD symptoms (35). In addition genetic studies implicated abnormalities in glutamate and *N*-methyl-D-aspartate (NMDA) receptor function in patients with OCD and their families (36). Reduction in the synapse associated protein 90 and postsynaptic density 95 associated protein 3 (SAPAP3) have been demonstrated to have a role in the pathogenesis of OCD with improvement in symptoms following restoration of these proteins (37, 38). The SLC1A1 gene, which encodes the excitatory glutamate amino acid transporter, and variants of the gene have been implicated in the transmission of OCD (39, 40). Moreover glutamate release inhibitors such as riluzole had a beneficial effect in patients with treatment resistant OCD (41). Similarly *N*-acetylcysteine which modulates the glutamate activity showed benefit in patients with OCD (42). Drugs acting on the NMDA receptors such as D-CYCLOSERINE and memantine have been shown to reduce the symptoms severity in patients with OCD (43–46). Therefore, pharmacological modulation of glutamate system has been shown to be useful in controlling the symptoms in patients with OCD and related disorders.

To develop appropriate surgical intervention it is prudent to understand the pathophysiology of the neural circuits associated with OCD and related disorders. Unlike the pathogenesis of movement disorders which is usually associated with hyper or hypo activity of a single surgical target/circuit such as loss of dopamine in Parkinson's disease, the pathogenesis of psychiatric disorders is more complex and involves dysregulation of multiple neural circuits/centers or targets. The success of neuromodulation in movement disorders is based on modulating these specific anatomical targets. Therefore, surgical intervention for psychiatric disorders requires a different strategy and approach than for movement disorders and involves modulating these multiple neural circuits to ameliorate clinical symptoms. Choosing a specific surgical target for psychiatric disorders requires a systematic approach with critical assessment of the available data in the literature. Based on this multicircuit model, the primary abnormality in OCD is the dysregulation of basal ganglia and limbic striatal circuits which modulates the neuronal activity in and between portions of the orbitofrontal and anterior cingulate cortex as well as the medial, dorsomedial, and anterior thalamic nuclei (17, 47). There are three components of this multicircuit model of OCD. In the first component, there is a reciprocal positive feedback loop from orbital and prefrontal cortex to the dorsomedial nucleus of thalamus via the anterior limb of internal capsule. Both the corticothalamic and thalamocortical pathways are excitatory and mediated by glutamate/aspartate and glutamate respectively (47, 48). The second component is primarily inhibitory in nature and involves interplay between the orbitofrontal/prefrontal cortex, the ventral caudate nucleus, the dorsomedial pallidum, and the thalamus (intralaminar, anterior, and dorsomedial nuclei) (15). In this component, the projections from ventral striatum to the dorsomedial pallidum involve neurotransmitters such as gamma-amino butyric acid (GABA) and substance P with the output from dorsomedial pallidum to the thalamus being primarily inhibitory in nature and mediated by GABA (49, 50). However, studies have also demonstrated a role for dopamine and glutamate in this second component (51). This second component also serves as a modulator for the excitatory first component. Additionally, this component also includes inhibitory serotonergic projections from the dorsal raphe nuclei of the midbrain to the ventral striatum (52). The third component involves the limbic system and the Papez circuit. Anxiety is one of the components of the symptomatology associated with OCD and the obsessions/compulsions in OCD have a significant impact on the patient's emotional status. In 1937, Papez emphasized the importance of cerebral cortex and hypothalamus in particular for experiencing the subjective emotions and proposed a circuit integrating these anatomic structures (53). His circuit begins from the hippocampal formation to the mammillary bodies via the fornix, which projects through the mammillothalamic tracts to the anterior thalamic nuclei with widespread connections to the cingulate gyrus. There are projections from the anterior cingulate to the striatal nucleus accumbens, which could mediate the emotional and anxiety component of OCD. As mentioned in the OCD model there are widespread connections between the Papez circuit and dorsomedial nuclei and orbitofrontal cortex. Integrating these three components, OCD symptoms are likely to occur when an aberrant positive feedback loop develops in the excitatory frontothalamic pathways that are inadequately inhibited/modulated by the striatopallidothalamic pathways. Therefore, obsessive/compulsive symptoms can occur with either abnormally increased activity in the orbitofrontothalamic pathways or decreased activity in the striatopallidothalamic pathways. Modulating either of these pathways can ameliorate the symptoms associated with OCD (24, 54, 55). In addition modulating the Papez circuit would take care of the disturbing emotional component of the obsessions/compulsions that patient with OCD experiences [(11, 56–59), see Fig. 38.2]. Functional imaging data do support this model as well as the role of CSTC loops in the pathogenesis of OCD. There is an evidence of increased activity and metabolism in orbitofrontal cortex, anterior cingulate cortex, and caudate in patients with OCD in both neutral and provoked states. Moreover, positron emission tomography (PET) and functional MRI (fMRI) studies demonstrated decreased metabolism in these anatomical structures following treatment with medications such as SSRIs or behavior therapy in patients with OCD (24, 60). These studies provide an insight into the areas of activation and response to treatment which may be useful in developing novel neurosurgical interventions for patients with OCD.

38.5. Mood or Affective Disorders

Major depressive disorder (MDD) is a common, debilitating psychiatric disorder with an estimated lifetime prevalence of approximately 9.5%. The primary medical treatment for MDD is SSRIs, with other second line antidepressant medications including monoamine oxidase (MAO) inhibitors, tricyclic antidepressants (TCA), and dual serotonin and norepinephrine reuptake inhibitors (SNRI); however, up to a third of patients do not respond to any of these medications. The current neurocircuitry model of depression is based on neuroimaging studies that demonstrate abnormalities in regional metabolic brain activity that normalizes with successful treatment. Frontal cortical abnormalities are most reproducibly found, including abnormalities in metabolism of the dorsolateral and ventral–lateral prefrontal cortex, orbitofrontal and ventromedial frontal cortices. Anterior and subgenual cortical changes are also seen, in particular, changes in Brodmann areas (BA) 24 and 25. Other anatomic substrates involved in these disorders include the amygdala, hippocampus, and the hypothalamic–pituitary axis (61). These disorders have affective, cognitive and neuroendocrinological components with their own individual neural circuits (17). The neural circuits that putatively modulate mood disorders can be classified into dorsal, ventral, and modulatory components (62).

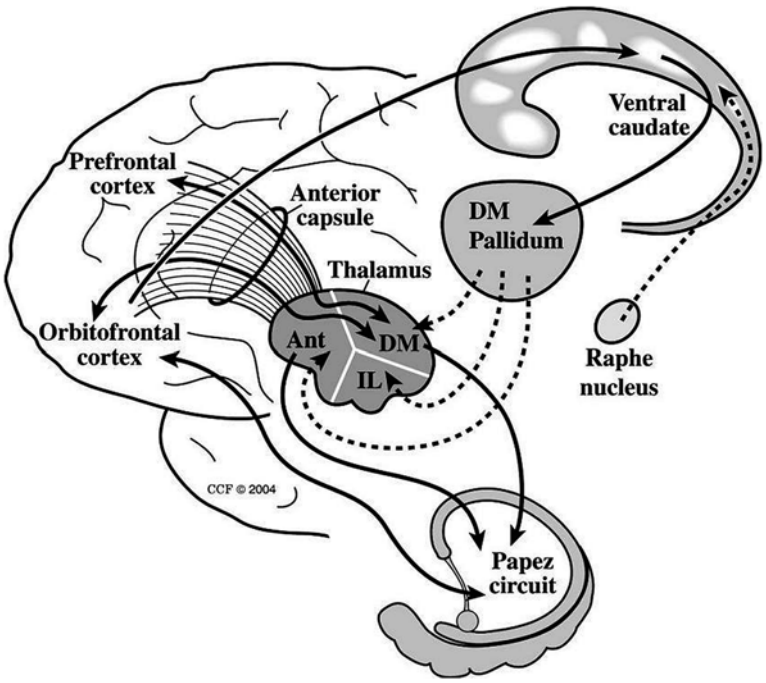

FIGURE 38.2. Schematic representation of neural circuits involved in the pathophysiology of Obsessive-compulsive disorders (OCD). Reprinted from: Kopell BH, Greenberg B, Rezai AR, Deep brain stimulation for psychiatric disorders, J Clin Neurophysiol 21:51–67, Copyright (2004) with permission from Wolters, Kluwer Health.

The dorsal or motor component consists of prefrontal, premotor cortex and dorsal anterior cingulate cortex which modulates the motor and cognitive components of mood disorders. This component projects from the dorsomedial portion of the pallidum to the thalamus. The ventral component modulates the affective component of these disorders and consists of the subgenual anterior cingulate (Brodmann's area 25), orbitofrontal, and insular cortices. This loop connects the ventral striatum through the medial/rostral pallidum to the thalamus. The modulatory component consists of pregenual anterior cingulate cortex, amygdala, and the hypothalamo-pituitary axis and modulates both dorsal and ventral components while subserving the neuroendocrine aspects of these disorders. Central amygdala, hippocampus, and hypothalamus control the release of neuroendocrine hormones such as cortisol, epinephrine, and others via stria terminalis (63), whereas basolateral amygdala modulates the motor and behavioral responses to emotional stimuli (64). These three components can be combined into a model similar to that proposed in the pathogenesis of OCD. Abnormal excitability and temporal patterning of activity in these parallel cortico-striato-thalamic-cortical pathways can be associated with depressive symptoms. These pathways include (a) dorsal cognitive thalamocortical loop consisting of prefrontal, premotor, and cingulate cortices and the anterior/dorsomedial thalamic nuclei, (b) ventral affective/limbic thalamo-cortical loop consisting of the cingulate cortex, the orbitofrontal cortex, and the anterior/dorsomedial thalamic nuclei, and (c) modulating circuit consisting of the amygdala and the hypothalamo-pituitary axis [(65, 66), see Fig. 38.3]. Though the results of functional neuroimaging is not as robust in patients with mood disorders as that with OCD due to the heterogeneity of the disease, however, PET and fMRI demonstrated abnormal metabolism in the OFC, basal ganglia, anterior cingulate gyrus, and amygdala in patients with mood disorders which tend to get reversed following treatment (61, 67–69). There is increased metabolism in orbitofrontal, anterior insular, amygdala, and subgenual cingulate cortices and decreased metabolism in dorsolateral prefrontal cortex and anterior cingulate cortex in patients with mood disorders (61, 69–72). These findings suggest an increased activity in the ventral pathways and decreased activity in the dorsal pathways, which might have important implications while selecting the targets for DBS such as dorsal targets for activation and ventral targets for deactivation (17, 73). DBS stimulation in an area where fibers from the dorsal and ventral pathways merge such as ventral anterior internal capsule could result in excitation of the dorsal pathways and inhibition of the ventral pathways resulting in a balanced or normal state (11). As mentioned, there is a paucity of animal models for mood disorders and OCD due to the inherent nature of these disorders. However, the introduction of Research Domain Criteria project, by the National Institute of Mental Health (NIMH) may provide a more suitable system to model human psychopathology in animals (74). A better understanding of this pathophysiology in animal models is the key factor in understanding human psychopathology and the development of more effective surgical interventions (75, 76). The abovementioned circuits are implicated in the symptoms of

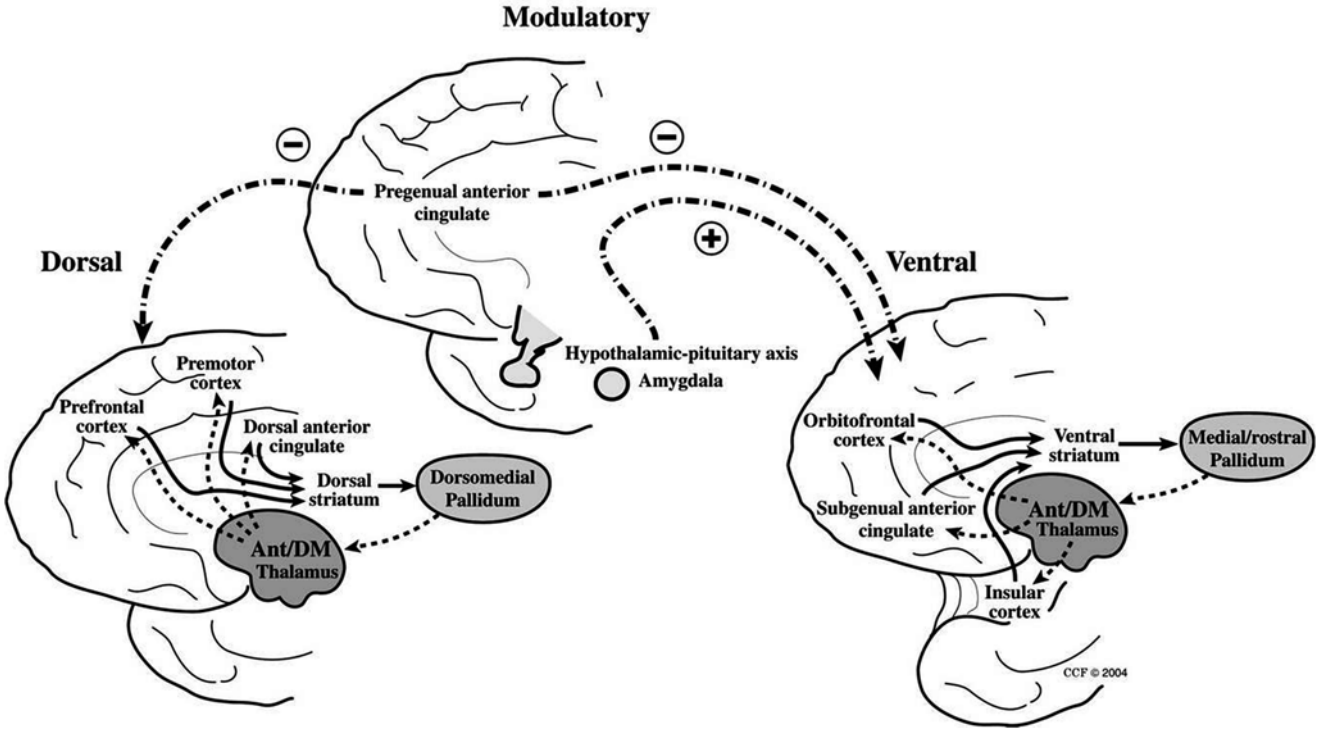

FIGURE 38.3. Schematic representation of neural circuits involved in the pathophysiology of Major Depressive disorders (MDD). Reprinted from: Kopell BH, Greenberg B, Rezai AR, Deep brain stimulation for psychiatric disorders, J Clin Neurophysiol 21:51–67, Copyright (2004) with permission from Wolters Kluwer Health.

depression, OCD and in emotional processing and generally have major influence on risk of development of psychopathology and might pave the way for the future development of novel surgical interventions and pharmacotherapy for these disorders (77). This model based therapy closely resembles that of therapeutic advances in PD.

38.6. Surgical Procedures in the Stereotactic Era

The introduction of stereotaxis in the latter half of the 20th century allowed precise placement of the subcortical lesions in the white matter tracts with minimal disruption of the cortical gray matter, thereby maintaining the efficacy of earlier crude surgical procedures while minimizing their side effects. Moreover, technological innovations such as functional imaging, physiological recordings, computer database and their integration with stereotaxis allowed even submillimeter accuracy in targeting the anatomical substrates. Due to the paucity of animal and control studies, majority of these studies are based on unrandomized and unblinded trials limiting the conclusions which can be drawn from these studies and thereby the widespread applicability of these procedures. Nonetheless, these procedures can provide some hope for the patients who are refractory to pharmacotherapy and have exhausted all other modalities of treatment. These procedures tend to modulate activity in the dorsolateral frontal, orbitofrontal, and cingulate cortices and their interactions with the basal ganglia and thalamus. Using stereotactic techniques, the following neurosurgical procedures were developed for the treatment of refractory psychiatry illnesses.

38.6.1. Cingulotomy

In 1942, Freeman and Watts first demonstrated that severing fibers from the cingulate gyrus led to an improvement in anxiety like states (11, 78). Whitty et al. reported the first bilateral cingulotomy in 1952, excising a segment of $4 \times 1 \times 1$ cm dimension from anterior cingulate gyrus on both sides of the brain (79). In 1962, Ballantine et al. (80) introduced stereotactic bilateral cingulotomies, localized using air-ventriculography and performed using electrically insulated thermistor electrodes in 273 patients (80). The lesion was typically performed 2–2.5 cm from the tip of frontal horns, 7 mm lateral to midline, and 1 mm above the roof of the ventricles bilaterally (11, 33). With the introduction of MRI in 1991, $1 \times 1 \times 1$ cm dimension cingulotomies

are being performed under its guidance with increased safety and accuracy. The safety and efficacy associated with stereotactic cingulotomies made it the most widely performed surgical procedure for refractory psychiatric disorders in the USA and Canada (33). These lesions affect the cortico-striato-thalamic-cortical (CSTC) loop by interrupting the reciprocal activity from the dorsal anterior cingulate cortex (ACC) to the orbitofrontal cortex, amygdala, and hippocampus via the cingulum (17, 81). Saxena et al. (17) reported a response rate of as high as 56% in patients with OCD following cingulotomies, though this study lacked robust psychiatric assessment tools (17). Ballantine et al. (80) reported symptomatic improvement in 25–50% of patients with OCD following cingulotomy (80). In 2002, Dougherty et al. (82) reported a prospective study carried out in 44 patients with OCD who underwent one or more cingulotomies following rigorous preoperative assessment. In this study, at a mean follow-up of 32 months, 32% of the patients met the criterion for treatment response and 14% were partial responders. Recent studies reported response rates of 36 and 48% in patients with OCD (83, 84). The response rates of this procedure in patients with affective disorders are more superior than that for OCD. Ballantine et al. (80) in their study of 120 patients with affective disorders reported significant response in greater than 60% of patients with 42% of patients becoming functionally healthy (80). In a recent study of 33 patients with severe treatment resistant major depression who underwent stereotactic cingulotomy followed by subcaudate tractotomy if necessary, reported an overall response rate of 33.3% as responders vs. 42.4% as partial responders and 24.2% as non-responders at mean follow-up of 30 months (85). Moreover, 41.2% were responders, 35.3% were partial responders and 23.5% did not respond to the treatment among those who underwent only cingulotomy in the same study (85).

This procedure is associated with very few adverse events with the incidence of hydrocephalus and seizures being similar to other stereotactic procedures. No deaths have been reported in more than 1,000 procedures performed at a center with hemorrhagic stroke rate of only 0.03% (11, 33). There are no significant permanent behavioral and cognitive deficits being reported following stereotactic cingulotomy for psychiatric disorders (86).

38.6.2. Anterior Capsulotomy

The procedure of anterior capsulotomy for refractory psychiatric illnesses was first developed by Leksell and Talairach in 1949. The procedure involves targeting the area between the anterior and middle third of the anterior limb of the internal capsule at the level of the foramen of Monro. The target lies 17 mm from the midline, 10 mm rostral to the anterior commissure and 8 mm above the intercommissural line. The lesion needs to be approximately 15–18 mm long and 4–5 mm wide (87). The lesion can be produced using either stereotactic radiofrequency or gamma radiation. The introduction of commercially available gamma knife in mid 1980s which can be coupled with the Leksell stereotactic system made it possible to translate the stereo CT images into the gamma knife treatment plans, thus further refining the surgical techniques (88). The anterior capsulotomy interrupts the ventral fibers from the orbitofrontal and subgenual anterior cingulate cortices en route via the anterior internal capsule to the medial, dorsomedial and anterior thalamic nuclei, thus ameliorating the clinical symptoms.

In previous studies, the response rates have been reported in the range between 48 and 78% following capsulotomy (86). However, a majority of these studies were retrospective in nature and lacked robust preoperative assessment tools. Greenberg et al. (86) demonstrated a response rate of 27 and 62% following a single and double shot of gamma knife capsulotomy bilaterally using modern measurement tools respectively. Liu et al. (89) reported that using modern assessment tools, 57% of the patients ($n=35$) were symptom free and 29% experienced significant improvement following bilateral capsulotomy (89). Similarly another prospective study reported a response rate of 60%, following bilateral lesions of the ventral portion of the anterior limb of the internal capsule at long-term follow-up (mean 10.9 years after surgery) (90). Anterior capsulotomy is a relatively safer procedure with no deaths directly associated with the procedure reported so far. Despite its safety, there are few reports of attempted suicide with one patient successfully committing suicide in the perioperative period (90). Transient side effects such as headache, confusion, urinary incontinence, weight gain, and lethargy have been reported with thermocoagulative capsulotomy. Nyman et al. (91) reported no significant changes in behavior or cognition in their series of 200 patients who underwent thermocoagulative capsulotomy (91). Ruck et al. (90) reported a single patient out of nine patients who developed radiation necrosis following bilateral gamma knife capsulotomy (90). This patient developed apathy, significant problems with executive functioning and memory. A mean weight gain of 6 kg and sexual disinhibition were also reported by this group. Greenberg et al. (86) reported 20% incidence of cerebral edema and headache, asymptomatic infarctions in caudate nucleus in 10% of the patients and frontal lobe dysfunction in 3% of the patients following gamma knife capsulotomy.

38.6.3. Subcaudate Tractotomy

Subcaudate tractotomy (innominotomy) was first described in 1965 by Knight in London, to relieve depression, anxiety, and obsessive symptoms and to minimize postoperative epilepsy and personality/cognitive changes (92, 93). This procedure aims to interrupt fibers from the orbitofrontal cortex to the thalamus via the striatum and the reciprocal connections from amygdala

to the OFC and subgenual ACC (17). Therefore, this procedure serves as a template for the approaches which tend to modify the subgenual ACC activity. Initially the lesions were created by placing multiple beta emitting rods (yttrium-90, half-life of 68 hours, 1×7mm in size), which generate lethal radiation and cause tissue necrosis to 1–5 mm from the surface of the rods. The target which is also known as substantia innominata, is located beneath the head of caudate nucleus and used to be localized with ventriculograms. In stereotactic era, the lesions are placed through the frontal burr holes above the frontal sinus and 15 mm from the midline. The lesion lies at the anteroposterior level of planum sphenoidale, being 20 mm long along the anteroposterior axis and 6–18 mm from the midline. Historically, two rows of four rods were placed to create the lesion which was later replaced by stereotactic radiofrequency thermocoagulation (94). The response rates of 55–66% and 50% have been reported in patients with depression and OCD respectively, who underwent subcaudate tractotomy (86). Bridges et al. (95) in their series of 1300 patients reported a favorable response rate of 40–60% who were able to live normal or near normal lives with continuation of medications. Moreover, this procedure also reduced the suicide rate to 1% postoperatively from 15% in cases of sever uncontrolled affective disorders without treatment (95). The common side effects of the procedure include headache, confusion, and lethargy which are minimal and transient (86). A single death has been reported which was attributed to yttrium lead migration (95). A mild long-term personality change was reported in 6.7% of 208 patients, which was not reflected in larger studies (95). Despite good outcomes and minimal side effects this procedure has fallen out of favor and is less frequently practiced than others.

38.6.4. Limbic Leucotomy

This procedure was developed by Desmond Kelly and Alan Richard in 1973 in London (96). Unlike the abovementioned three procedures, limbic leucotomy aimed at interrupting white fibers at two separate areas, the fronto-thalamic loop and the Papez circuit. The procedure involves interrupting the fronto-thalamic loop in the lower medial quadrant of each frontal lobe using three 6 mm thermocoagulative or cryogenic lesions and a 6 mm lesion in the cingulum bilaterally (Subcaudate tractotomy and cingulotomy).

Mitchell Higgs et al. ($N=66$) reported that 76% of patients improved clinically at 6 weeks and 76% at 16 months, following this procedure (97). Montoya et al. ($N=21$) reported favorable response in 36–50% of patients with intractable major depression and OCD using modern diagnostic and assessment tools (98). Cho et al. (99) reported a response rate of 68.8% following radiofrequency thermocoagulation limbic leucotomy which remained stable at a 7 year follow-up (99).

Adverse effects include transient headache, confusion, amotivation, perseverative behavior, lethargy, apathy, and incontinence with no deaths or seizures (97). One patient in a series of 66 patients developed severe memory impairment due to inappropriate placement of the lesion, whereas 12% had lethargy at an average follow-up of 16 months (97). A significant number of patients lost weight in this study either because of clinical improvement or reduction in medications. These side effects were mirrored in other studies as well (98).

38.7. Deep Brain Stimulation for Psychiatric Disorders

In 1960, Hassler et al. (100) reported that the low frequency stimulation of basal ganglia could worsen tremors whereas high frequency stimulation could ameliorate them. This observation led to the origin of neurostimulation therapy for a variety of motor disorders. Following the success of deep brain stimulation therapy for movement disorders, there has been an intense interest in the stimulation therapy for refractory psychiatric disorders as well.

In 1979, Dieckmann et al. reported improvement in phobias and obsession symptoms following placement of an electrode near the parafascicular complex in the intralaminar thalamic nuclei and stimulation at low frequency (5 Hz) at 1-year follow-up (33). Similarly, Heath et al. stimulated the cerebellar vermis to treat psychiatric disorders focusing on the neural circuitry rather than a specific target (101). Stimulation of the cerebellar vermis upregulated the septal activity and inhibited the amygdala activity, thereby ameliorating the symptoms of intractable behavioral disorders and epilepsy (102). In another study of 135 patients in which subcortical electrical stimulation was applied to various surgical targets, emotional responses were obtained most frequently from the cingulum and genu and least frequently from the anterior capsule and subcaudate regions (103). Preliminary results suggested the efficacy of this treatment modality in the management of treatment resistant psychiatric disorders such as OCD and MDD with neurostimulation therapy is likely to become a mainstay in the management of these disorders Table 38.1. However, the targets for stimulation therapy are often the sites where ablative therapy has already suggested efficacy.

Deep brain stimulation of the subthalamic nucleus and globus pallidus interna for the treatment of Parkinson's disease were first approved by Food and drug administration in 2002 and 2003 respectively. In addition to improvement in motor symptoms of Parkinson's disease, stimulation of STN is often associated with improvements in neuropsychological symptoms (15). Since

Table 38.1. Medically refractory psychiatric disorders potentially benefitted by Deep Brain stimulation (DBS) in various research studies.

1	Obsessive-compulsive disorder and Tourette syndrome
2	Major depressive disorder
3	Addictions and alcoholism
4	Eating disorders (obesity and anorexia nervosa)
5	Posttraumatic stress disorder
6	Dementias including Alzheimer disease and cognitive dysfunctions
7	Impaired conscious state

STN is one of the components of limbic, dorsolateral prefrontal and orbitofrontal loops, stimulation of STN for Parkinson's disease is often associated with improvement in mood, anxiety, and obsessive-compulsive symptoms (104–106). Similarly, there are reports of mirthful laughter and hilarity following STN DBS for Parkinson's disease at supratherapeutic stimulation (107). The medial and ventromedial portions of the STN and surrounding structures such as lateral hypothalamus or ventral tegmental area, substantia nigra, and zona incerta may be involved in this phenomenon. Studies have documented that stimulation of either of these structures (medial/ventromedial STN, lateral hypothalamus, or ventral tegmental area) is associated with activation of dopaminergic and serotonergic structures of the medial forebrain bundle whereby direct stimulation induces feelings of pleasure (108).

In addition, there are reports of transient acute depression induced by high frequency stimulation of STN DBS (109, 110). In contrast to this, episodes of hypomania, mania, improvement in anxiety and psychosis have been documented following stimulation of STN DBS for Parkinson's disease (111, 112). Similarly DBS of the globus pallidus has been reported to be associated with anxiolytic and antidepressant effects in patients with dyskinesias (113, 114).

38.7.1. Surgical Technique for Implantation of DBS

DBS implantation surgery is usually performed as a two-stage procedure. Briefly, Stage 1 involves stereotactic guided implantation of DBS electrode into deep anatomical targets, under monitored anesthesia. Following attachment of stereotactic Leksell frame (Elekta Inc., Atlanta, GA) to the patient's head under sedation and local anesthesia, CT scan using stealth protocol (1-mm contiguous cuts) is carried out. These CT scan images are then fused to the preoperative MRI using StealthStation to acquire the coordinates of the target and a safe surgical trajectory is planned on the stealth station. The entry point on the skull as defined by the Leksell frame coordinates is prepared in a usual manner and a 14 mm burr hole is made at the point of entry of the cannula. The Navigus Stimloc™ Burr Hole Cover system (Medtronic, Minneapolis, MN, USA) is attached over the burr hole to secure the DBS lead following placement. The underlying dura mater and pia mater are coagulated and opened at the predetermined entry point. A cannula of 177 mm length is inserted through the pial opening to 15 mm above the target. A microelectrode is introduced through the cannula for microelectrode recording to delineate the anatomical target. A single or multiple tracts are used to define the boundaries based on kinesthetic and macrostimulation responses. Following satisfactory delineation of target, a DBS lead (Medtronic, Minneapolis, MN, USA) is implanted, connected to the temporary extension wire and tunneled under the scalp in the parietal region. A week later, stage 2 is performed under general anesthesia in a day care surgery unit. This procedure involves tunneling the extension wire under the scalp and skin of neck and connecting the distal end of this extension wire to the pulse generator which is placed in the subcutaneous pocket in the subclavicular or abdominal area. Subsequent programming is performed 3–4 weeks after surgery and is titrated according to the patient symptoms.

38.7.2. DBS for OCD, Tourette Syndrome, and MDD

Despite the widespread use of DBS therapy for movement disorders, there are few studies documenting the efficacy of this therapy for treatment resistant psychiatric disorders. So far, this therapy has been reported in 100 patients with OCD, 50 patients with depression and 40 patients with Tourette syndrome with more than 50% response rates in OCD and depression respectively (33, 115). This paucity of data on DBS for psychiatric disorders can be attributed to the regulations involved and lack of stringent assessment criterion for patient enrollment. The only psychiatric disorder for which DBS is approved by the FDA is OCD which has been granted a humanitarian device exemption status (33). Moreover, the delay in response following stimulation and the risk of inducing hypomania in depressed patients warrant frequent follow-ups and close proximity to the programming physician especially for patients travelling from distant places where such facilities are not available. Nuttin et al. (116) and Vandewalle et al. (117) first reported the DBS treatments for OCD and Tourette syndrome respectively in 1999. In the first

report, they stimulated the anterior limb of the internal capsule of four patients with resistant OCD with target coordinates being identical to those aimed for capsulotomy. This stimulation led to symptomatic improvement in three out of four patients. Despite lack of stringent assessment and availability of scores with regard to changes in mood and obsessive-compulsive symptoms, one of the patients reported more than 90% improvement in her compulsive symptoms after 2 weeks of stimulation. In 2003, Nuttin et al. using Y-BOCS, global assessment of function (GAF) score, as well as double blind clinical assessment, reported that the capsular stimulation led to the reduction in core symptoms, 21 months after surgery in six patients with severe treatment resistant OCD (118, 119). They reported that the location of the tip of the electrode in a patient with the best clinical response was placed at 13 mm lateral to the midline on the right, 14 mm lateral to midline on the left, 3.5 mm anterior to the anterior commissure at the level of intercommissural plane. Of note, electrode contacts 1 and 2 were in the internal capsule, whereas the bottom or electrode contact "0" was in the region of the nucleus accumbens and the top electrode contact "3" was dorsal to the internal capsule. Using this target and constant stimulation, three out of six patients responded with 35% reduction in Y-BOCS score. One patient had less than 35% improvement on Y-BOCS and therefore was considered as nonresponder and the other two patients never made it to the assessment phase. There was significant worsening of mood and obsessive-compulsive symptoms in responding patients in the "off" state who returned to the baseline and improvement in the "on" state. In addition, the responders demonstrated decreased frontal metabolism on PET scan, following 3 months of bilateral stimulation. Subsequent details of follow-up studies of these patients and two additional patients were published in 2008 (118). There were no complications related to the implantation such as hemorrhage, infection or death reported in this study. Neither changes in vegetative states or manic behaviors was documented during this study. However, some cognitive changes and behavior disinhibition was reported in two patients with high amplitude stimulation which responded to decrease in stimulation intensity. In a double-blind, cross over, multicenter study assessing the efficacy and safety of stimulation of the STN in 16 patients with highly refractory OCD, it was reported that there was significant decrease in Y-BOCS scores along with increase in global assessment of function scores in patients who underwent STN stimulation as compared to sham stimulation (120). However, depression, anxiety, and other ratings of neuropsychological measures did not change by STN stimulation. Apart from STN, other areas such as internal capsule, zona incerta, substantia nigra, and Forel field were unexpectedly stimulated due to placement variations in patients who benefitted from this stimulation. In addition, there were a total of 15 serious adverse events, including one case of intracerebral hemorrhage leading to permanent finger palsy, two infections with transient motor and psychiatric symptoms and 23 nonserious adverse events in this study. Some transient psychiatric symptoms were reported during sham stimulation as well. Recent studies documented >60% response rates with significant improvement in Y-BOCS scores in patients undergoing deep brain stimulation of anterior limb of the ventral capsule and adjacent ventral striatum (VC/VS) for severe and treatment-refractory OCD (121, 122). In addition, depressive symptoms improved significantly in this group as a whole. A total of 23 adverse events in 11 patients were reported in this study including two small intracerebral hemorrhages without long-term sequelae, one lead/extension breakage, one seizure event after the procedure and one case of wound infection. In addition, there were a total of nine adverse events associated with stimulation including four incidents of increased depression or suicidal ideation in three patients. Another double blind sham controlled study investigating the efficacy of unilateral deep brain stimulation of the right nucleus accumbens in patients with refractory OCD reported that 50% of the patients reached at least partial response after the first year post-treatment (123). However, only one out of ten patients had >35% decrease in Y-BOCS score. They also reported improvement in depression, global functioning and quality of life within 1 year with no significant changes in anxiety, global symptom severity, and cognitive function during the study period. There were few adverse events reported in this study. Bilateral deep brain stimulation of nucleus accumbens yielded a mean Y-BOCS decrease of 72% in 9 out of 16 patients in a sham controlled double blind crossover phase study (124). Moreover, they reported the mean Y-BOCS score difference of 25% between active and sham stimulation. In addition, depression and anxiety symptoms decreased significantly following the stimulation in this study. Few adverse effects such as mild forgetfulness, word-finding problems, hypomania, numbness at incision site or feeling of DBS leads, wound infection, but no permanent adverse events were reported in this study. Recently, Nair et al. (125) proposed the anteromedial (limbic) globus pallidus internus (Gpi) as a potential surgical target for the treatment of patients with Tourette's syndrome and severe OCD and supported its further investigation as a target for the treatment of refractory psychiatric disorders (125). They reported four patients with Tourette's syndrome who underwent DBS implantation for their movement disorder and achieved >85% improvement in their OCD symptoms on obsessive-compulsive inventory scale (OCI). Similarly Mayberg et al. (126) implanted bilateral DBS in Broadmann area 25 in six patients with refractory depression and reported that the chronic stimulation of white matter tracts adjacent to the subgenual cingulate gyrus was associated with a significant and sustained remission of depression in four out of six patients (126). The antidepressant effect of this stimulation was demonstrated with a marked reduction in local blood flow and changes in limbic and cortical sites on PET scans. Moreover, four out of these six patients maintained response and two met remission criterion according to this study. Two patients had persistent surgical site infection which led to removal of DBS leads at 6 months follow-up. In their subsequent study of 20 patients with treatment resistant depression with a follow-up of 3–6 years they reported the average response rates of 62.5, 46.2, and 75% at 1,2 and 3 years after DBS implantation respectively (127). Moreover at the last

follow-up (3–6 years) the average response rate was 64.3% with progressive improvement in the social functioning and physical well-being. In terms of adverse events, six patients had hospitalizations for worsening depression and suicidal ideation and of these, two patients were successful in committing suicides; another four patients had wound infections. Recently Lozano et al. (128) reported a multicenter study of 21 patients with severe depression who underwent bilateral implantation of subcallosal cingulate cortex and reported a response rate of >60% after 12 months of DBS (128). Other study implanting DBS electrodes at the similar target for ten patients with major depression and seven patients with bipolar disorder reported a remission and response rate of 18% and 41% after 24 weeks, 36% and 36% after 1 years, 58% and 92% after 2 years of active stimulation with no significant differences between MDD and those with bipolar disorders (129). Adverse events in this study included one patient with bilateral infected leads leading to removal of DBS leads, anxiety in two patients, worsening depression in one patient, suicidal ideation in one and suicidal attempt in each of two others. Another study investigated the efficacy of bilateral DBS of the ventral capsule/ventral striatum (VC/VS) for the treatment of refractory depression in 15 patients (130). Using Hamilton Depression Rating Scale-24 item (HDRS) and the Montgomery-Asberg Depression Rating Scale (MADRS), the response rates at 6 months and at last follow-up was 40% and 53.3% and 46.7% and 53.3%, respectively. Moreover, the remission rates were 20% and 40% at 6 months and at last follow-up respectively using the HDRS in this study. Adverse events such as lead fracture, hypomania, syncopal episodes, increased depression/suicidal ideation and insomnia were reported in this study. A double blind study assessed the efficacy of bilateral DBS in the nucleus accumbens for the treatment of refractory major depression in three patients (131). This study also investigated the brain metabolism 1 week before and 1 week after stimulation onset. Using functional PET scan, they observed significant changes in brain metabolism as a function of stimulation in fronto-striatal networks. They concluded that DBS to the nucleus accumbens might help in alleviating the dysfunction of "reward system" and hence can be a hypothesis-guided approach for refractory major depression. Later on they reported antidepressant and antianhedonic effects of DBS to nucleus accumbens in ten patients suffering from treatment resistant depression (132). This study reported 50% reduction of the HDRS at 12 months following stimulation and three patients achieved remission for 1 month. Few adverse events such as anxiety, pain, erythema, sweating, dysphagia, eye swelling, attempt to suicide, and completed suicide were reported in this study.

Other targets such as lateral habenula and inferior thalamic peduncle have been reported as case reports in non-blinded trials for the treatment of refractory depression (133, 134).

38.7.3. DBS for Addiction and Eating Disorders

In 1976, Quadde et al. (135) stereotactically stimulated and electrocoagulated portions of the lateral hypothalamus in three obese patients with successful outcome. Dysfunction of the "reward circuit" has been implicated in the underlying pathophysiology of overeating and addiction disorders and thus became a target for DBS (136) (see Fig. 38.4a, b). Lateral hypothalamus, ventromedial hypothalamus, and nucleus accumbens are the relay stations in "reward circuit" and thus are the potential DBS targets for these disorders (137). Animal studies have reported that DBS of the nucleus accumbens shell attenuates cocaine priming-induced reinstatement of drug seeking in rats and may be a potential therapeutic option in the treatment of severe cocaine addiction (138). Kuhn et al. (139) reported significant alleviation of alcohol dependency in one patient who underwent bilateral DBS of the nucleus accumbens for severe anxiety and secondary depressive disorder. Later, the same group reported a higher rate of successful smoking cessation (30%) compared to unaided cessation in the general population (8.7%) in ten patients who were also smokers and were treated for Tourette's syndrome, obsessive-compulsive disorders, or anxiety disorders by DBS of the nucleus accumbens at 30 months follow-up (140).

38.7.4. DBS for Posttraumatic Stress Disorder (PTSD)

Studies have implicated greater activation of amygdala and anterior cingulate cortex with lesser activation of hippocampus and ventromedial prefrontal cortex in patients with PTSD as compared to normal individuals (141–143) (see Fig. 38.5). Moreover, animal studies have reported alleviation of PTSD symptoms in a rat model, following DBS of the amygdala (144). These findings paved the way for the neuromodulation of amygdala and fronto-striatal circuits in the management of patients with refractory PTSD.

38.7.5. DBS for Impaired Conscious State

With the advances in neuroimaging and our understanding of the specific pathways and the sites of neural dysfunction, the frontiers of neuromodulation are likely to widen and can involve modulation of the state of mind and conscious state itself.

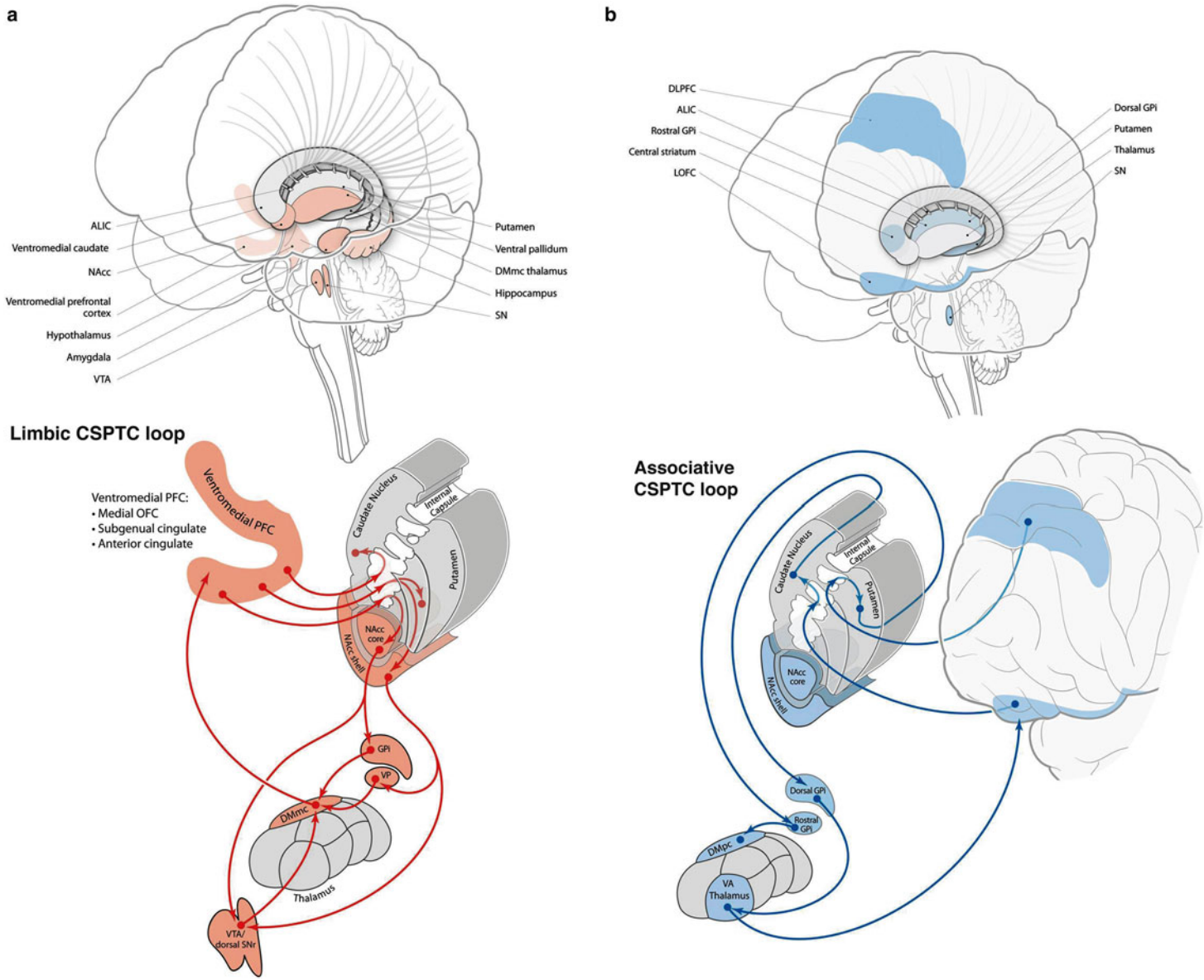

FIGURE 38.4. Schematic representation of neural circuits involved in the pathophysiology of obesity. (**a**) The limbic or "reward" cortico-striato-pallido-thalamo-cortical (CSPTC) loop and (**b**) the associative or "cognitive" CSPTC loop. *ALIC* anterior limb of internal capsule, *NAcc* nucleus accumbens, *VTA* ventral tegmental area, *DMmc* dorsomedial magnocellular thalamus, *SN* subthalamic nucleus, *PFC* prefrontal cortex, *OFC* orbitofrontal cortex, *VP* ventral posterior thalamus, *Gpi* globus pallidus internus, *DLPFC* dorsolateral prefrontal cortex, *LOFC* lateral orbitofrontal cortex, *VA* ventral anterior thalamus, *DMpc* dorsomedial parvocellular thalamus. Reprinted from: Taghva A, Corrigan JD, Rezai AR, Obesity and brain addiction circuitry: implications for deep brain stimulation. Neurosurgery. 71:224–238, Copyright (2012) with permission from Wolters Kluwer Health.

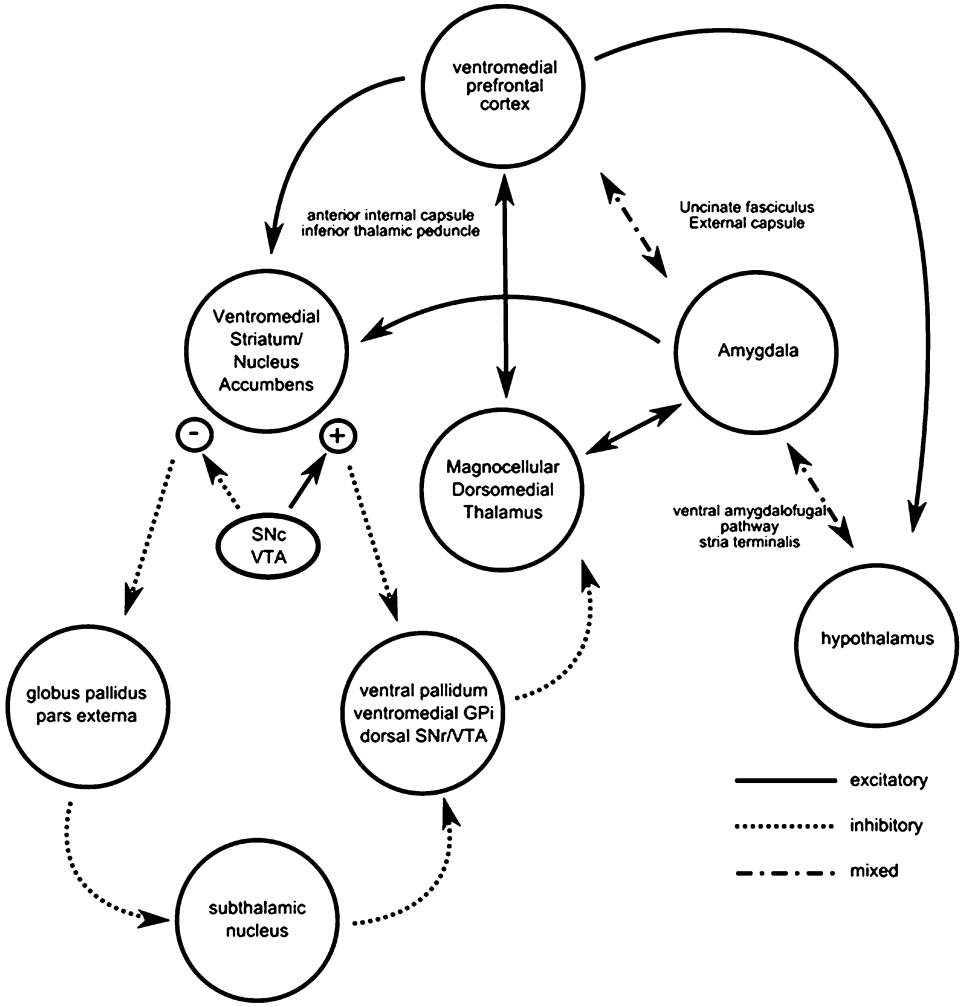

FIGURE 38.5. Schematic representation of neural circuits involved in the pathophysiology of PTSD. The limbic cortico-striato-pallido-thalamo-cortical loop is displayed on the *left* involving the ventromedial prefrontal cortex, ventromedial striatum/nucleus accumbens, globus pallidus pars externa, subthalamic nucleus, ventral pallidum, ventromedial Gpi, dorsal SNr, and ventral tegmental area (VTA). Another circuit on the *right* involves the connections between ventromedial prefrontal cortex, amygdala and hypothalamus. Reprinted from: Taghva A, Oluigbo C, Corrigan J, Rezai AR, Posttraumatic stress disorder: neurocircuitry and implications for potential deep brain stimulation, Stereotactic Funct Neurosurg. 91:207–219. Copyright © 2013 Karger Publishers, Basel, Switzerland.

Schiff et al. (145) reported that the bilateral DBS of the central thalamus modulates behavioral responsiveness in a 38 year old patient who remained in minimal conscious state (MCS) for 6 years following traumatic brain injury (145). The anterior interlaminar thalamic nuclei and paralaminar regions of the association nuclei were the DBS targets in this study. Following stimulation, this patient had significant improvement in limb control, arousal, and oral feeding as compared to off state. This study suggested that DBS can promote significant late functional recovery from severe traumatic brain injury. Yamamoto et al. (146) implanted DBS at the same targets in 21 patients with vegetative state following traumatic head injury and reported that 8 of the 21 patients emerged from the vegetative state and were able to obey verbal commands. However, all patients except one were bedridden. Another study of 25 cases with similar targets for persistent vegetative states, reported that it was not certain that DBS was directly responsible for the positive changes observed as long-term spontaneous recovery is anticipated and documented in these patients (147). The conflicting results in these trials or studies may be attributable to the heterogeneity of the patient population enrolled in these studies as patients with significant cortical or subcortical damage are less likely to improve vs. those with isolated damage to the central arousal centers.

In addition, Hamani et al. (148) reported memory enhancement in a patient who underwent bilateral hypothalamic deep brain stimulation for morbid obesity. The hypothalamic stimulation modulated activity in limbic system and improved certain mem-

ory functions such as autobiographical memories. Recently, Laxton et al. (149) in phase I trial of six patients with mild Alzheimer's disease who received continuous stimulation of bilateral hypothalamus/fornix reported improvements and/or slowing in the rate of cognitive decline at 6 and 12 months in some of the patients. These findings have opened the door to a new realm of neuromodulation so as to enhance the cognitive/memory functions in patients with dementia.

38.8. Other Surgical Techniques

38.8.1. Vagal Nerve Stimulation and Transcranial Magnetic Stimulation

Vagal nerve stimulation (VNS) has been shown to be efficacious in patients with chronic and refractory depression and is being investigated for other anxiety disorders (150, 151). In 2005, VNS was approved by FDA as an adjunct treatment for medical refractory depression in patients older than 18 years of age (152). The surgical technique of VNS implantation is similar to that used for treating refractory epilepsy (153). Briefly, VNS system (Cyberonics Inc., Houston, TX, USA) consists of helical electrodes and a pulse generator. A longitudinal surgical incision is taken along the anterior border of sternocleidomastoid and the vagus nerve is exposed by using blunt tissue dissection. After exposing the vagus nerve, two helical electrodes are wrapped around the nerve and distal end of electrodes are tunneled under the skin of the neck into the subclavicular region. The distal ends of electrodes are connected to the pulse generator which is subsequently placed in the subcutaneous pocket. After few weeks of recovery the pulse generator is programmed in a graduated manner until the therapeutic effect or maximal tolerable level is reached.

TMS has been evaluated for refractory depression, schizophrenia, obsessive compulsive disorder, and neuropathic pain with varied success (154–158). rTMS for medical refractory depression in adults was approved by FDA in 2008 (152). This therapy involves passage of electric current through a magnetic coil which is tangentially oriented to the scalp in the anterior–posterior direction and induces a brief and localized magnetic field in the region being exposed. TMS activates or inhibits various cortical and subcortical neural networks by generating magnetic field that penetrates the skull of the patient. TMS also modifies the synaptic characteristics of these neural networks (159). High frequency stimulation (>5 Hz) increases the cortical excitability whereas low frequency stimulation (<5 Hz) has inhibitory control on the neural circuits (160). Repetitive TMS stimulation of the dorsolateral prefrontal cortex has been shown to have antidepressant effects (161). It is difficult to accurately estimate the area of activation and stimulation parameters due to variation in cortical geometry, current generated, cerebral plasticity, membrane potentials, and ion channel activity (162, 163).

38.9. Ethical Considerations

Though DBS is an efficacious surgical treatment for medically refractory psychiatric disorders such as OCD and MDD, it is prudent to follow a sequence of safety measures and ethical considerations to ensure proper execution and favorable outcome (164). There are many ethical concerns which need to be addressed so as to permit the appropriate evaluation of this modality for a variety of psychiatry disorders. First, appropriate criteria for selection of patients need to be established and informed consent obtained. All patients must meet the standard criterion for chronic, severe/disabling and treatment-refractory OCD or affective disorders (AD) as outlined by DSM-5 (Diagnostic and Statistical Manual 5) (165). Moreover, quantitative psychiatric assessment using accurate battery of tests such as Yale-Brown obsessive-compulsive scale and Hamilton-depression scale must be considered so as to maintain uniformity across research studies. A close collaboration with an experienced psychiatrist is mandatory in proper selection of a patient for a particular study. In addition to a psychiatrist, the assessment committee should consist of a neurologist, a functional neurosurgeon (trained in stereotactic and functional neurosurgery), neuropsychologist, bioethicist, and lay personnel. The role of this assessment committee is to ensure appropriate patient selection and patient counseling while enrolling these patients in clinical trials/research studies. After appropriate patient selection, a multidisciplinary team consisting of experienced functional neurosurgeons, neurologists, and psychiatrists should conduct a particular study/procedure (11). The research study protocol must be approved by the Investigative Review Board and additional review by the FDA for an investigational device exemption must be considered (166). The use of DBS for psychiatric disorders must be limited to patients who are capable of decision-making and are able to opt out of the study. The study should be carried out only to ameliorate disabling psychiatric symptoms and should not be enforced by law, political, or social reasons. In addition, ethical issues such as use of DBS in pediatric patients, inadvertent use of DBS therapy to alter patient's personal identity, for brain enhancement or for behavior modification must be addressed prior to any research study (167).

38.10. Conclusion and Future of Psychosurgery

DBS with its ability to reversibly modulate the nervous system is an option that can be safe and effective in improving the outcomes in patients with severe OCD and MDD. However, additional longer-term studies and randomized controlled trials are needed in order to facilitate a more widespread use of DBS for those with OCD and MDD. DBS for other psychiatric disorders is still at the very early stages of evolution and needs further exploration with regard to safety and benefits. Surgery for psychiatric disorders needs to be performed in collaboration with an expert group of multidisciplinary specialists managing these complex patients. Our improved understanding of the neural circuits and pathophysiology underlying these psychiatric disorders will guide the future of neuromodulation for psychiatric disorders. The beneficial effect that DBS has on these circuits locally and at a distance in the brain may contribute to further our understanding of these networks. To optimally treat or modulate different subtypes of MDD and functions such as emotions and behaviors, we need to aim multiple physiological "targets" and neural circuits instead of a single anatomical target. With technological advances and increased understanding of the basic pathophysiology of psychiatric disorders, it is likely that more precise and limited amount of nervous tissue will be targeted. Availability of scheduled stimulation devices or closed loop stimulation devices can further enhance the efficacy of this therapy for refractory psychiatric disorders. In addition, these surgical approaches can destigmatize psychiatric disorders by describing the biological and physiological etiologies and the neural circuits involved (33).

Ongoing research and technological advances are likely to unveil more refined surgical targets and better stimulation protocols which help in maximizing the clinical benefits while minimizing the risks/side effects associated with DBS. An interdisciplinary approach with strict ethical consideration needs to be implemented in managing these difficult to treat disorders. With appropriate use of technology and strict adherence to protocols we are likely to help more patients suffering from refractory psychiatric disorders.

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39
Rating Scales for Psychiatric Disorders

Martha Sajatovic, M.D., Mark Opler, Ph.D., M.P.H., Alexandra Junewicz, M.D., and Lewis Opler, M.D., Ph.D.

Abstract A large body of literature describes clinical and research instruments to evaluate patients with psychiatric illness along specific dimensions of symptom expression, comorbidity, and multiple other health outcomes. The use of rating scales in clinical practice and in research standardizes approaches for diagnosis and assessment. This chapter will review some of these rating scales within common diagnostic categories such as mood and psychotic disorders, post-traumatic stress disorder (PTSD) and anxiety disorders. Additional discussion will cover use of rating scales in clinical and research settings and future directions in the application of standardized rating scales. While there is a considerable body of literature on the many ways to use rating scales to measure a variety of important health domains, much work still needs to be done to optimize use of rating scales in advancing clinical practice and research. Standardized instruments can help in identifying individual or groups of individuals in order to quickly and efficiently deliver treatment that is appropriate for a given individual. The more standardization can be achieved, the easier it will be to compare individuals or groups of individuals and assess the relative quality of care and outcomes across care settings.

Keywords Rating scales • Clinical trials • Outcomes • Measurement • Psychometric properties

39.1. Introduction

The introductory text of the Diagnostic and Statistical Manual, 5th Edition (DSM-5) defines a mental disorder as, *"A syndrome characterized by clinically significant disturbance in an individual's cognition, emotion, regulation or behavior that reflects a dysfunction in the psychological, biological or developmental processes underlying mental functioning"* (1). This definition emphasizes the comprehensive and multiple elements that comprise mental health and mental illness. A challenge to the field is how to accurately and reliably classify the various mental disorders, assess their relative severity and impact on functioning and quality of life, as well as being able to evaluate change over time. Classification systems such as DSM-5 provide some guidelines for separating diagnoses and assessing and qualifying clinically relevant sub-groups.

M. Sajatovic, M.D. (✉)
Professor, Departments of Psychiatry and Neurology, Case Western Reserve University,
Director, Neurological and Behavioral Outcomes Center, University Hospitals of Cleveland, Cleveland, OH, USA
e-mail: martha.sajatovic@uhhospitals.org

M. Opler, Ph.D., M.P.H.
Assistant Professor, Departments of Psychiatry and Environmental Medicine, New York University School of Medicine,
New York City, NY, USA
e-mail: Mark.Opler@nyumc.org

A. Junewicz, M.D.
Resident, Department of Psychiatry, New York University School of Medicine, New York City, NY, USA
e-mail: Alexandria.Junewicz@nyumc.edu

L. Opler, M.D., Ph.D.
Clinical Professor, Department of Psychiatry, Columbia University College of Physicians and Surgeons, New York City, NY, USA
e-mail: mgo4@columbia.edu

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Specifiers describe general severity as "mild", "moderate", "severe" or "extreme" (1). While these classifications are useful, they have a number of limitations in the assessment of specific dimensions of functioning that may be a focus of treatment. A large body of literature describes clinical and research instruments to evaluate patients with psychiatric illness along specific dimensions of symptom expression, comorbidity, and multiple other health outcomes. This chapter will review some of these instruments within common diagnostic categories such as mood and psychotic disorders, post-traumatic stress disorder (PTSD) and anxiety disorders. Additional discussion will cover use of rating scales in clinical and research settings and future directions in the application of standardized rating scales. It should be noted that some scales are copyrighted instruments and individuals using scales, especially for commercial purposes should check on access and availability.

39.2. Rating Scales in Schizophrenia

Schizophrenia and related psychotic disorders are recognized as being serious, persistent brain disorders with a high degree of heterogeneity, marked by changes over the life-course of the individual. While some advances have been made in our understanding of the etiology of schizophrenia (2), translation of our understanding of the neurobiology of this disease into actionable treatment targets remains elusive. In addition to positive symptoms (e.g. delusions, hallucinations), individuals with schizophrenia are often characterized by negative symptoms, lack of affective response, loss of volitional drives, as well as depression, cognitive dysfunction, and a host of other issues that result in reduced qualify of life and role functioning.

In keeping with the multi-dimensional nature of the disorder, there are a wide range of types of assessments and outcome measures utilized in research and clinical practice for patients with schizophrenia. Some are administered by clinicians following a guided interview or examination while others are self-administered questionnaires. These can be further classified into several basic groups:

Broad Spectrum Symptom Severity: These assessments typically cover a wide range of symptoms, allowing the clinician to obtain an overall index of severity. These measures are broadly applicable, allowing for assessment of treatment efficacy over time within subjects, provide comparative descriptions of symptom profiles, and serve many other purposes.

Domain Specific Scales: By contrast to the generalized measures, these tools focus on one specific dimension of a given disorder, e.g. depression, negative symptoms, functional impairment, quality of life, and many others. These measures typically are used to screen for a specific patient subtype, to help test for or manage the emergence of a challenging domain of pathology or dysfunction.

Global Assessments of Illness: These tools are either components of or modeled on the Clinical Global Impressions Scale (3) and are highly accessible, simple tools for describing clinical improvement or deterioration.

Side Effect Rating Scales: These measures are used to evaluate one or more of the side effects that may occur as a result of antipsychotic treatment. They include measures of motor and non-motor side effects, with a focus on extrapyramidal symptoms.

Table 39.1 illustrates selected rating scales for assessment of individuals with schizophrenia. These brief descriptions can be supplemented by the published manuals or other resources for each of the measures below:

TABLE 39.1 Selected rating scales for schizophrenia.

Scale name and acronym	Key features	Reference	Source for further information
The Positive and Negative Syndrome Scale (PANSS)	• 30 items, most widely used schizophrenia tool • Semi-structured interview guide (SCI-PANSS) • 8-item version for remission (SCI-SR)	Kay SR, Fiszbein A, Opler LA. The Positive and Negative Syndrome Scale (PANSS) for schizophrenia. Schizophr Bull. 1987;13:261–276	The PANSS Institute—www.panss.org
The 4-Item Negative Symptom Assessment (NSA-4)	• Brief, easy-to-score tool for negative symptoms • Derived from and comparable to 16-item version • May be used by wide range of mental health professionals • Requires very minimal training	Alphs L, Morlock R, Coon C, van Willigenburg A and Panagides J. The 4-Item Negative Symptom Assessment (NSA-4) Instrument: A Simple Tool for Evaluating Negative Symptoms in Schizophrenia Following Brief Training. Psychiatry. 2010; 7(7):26–32	Contact the author directly; lalphs@jnj.its.com
Drug-induced Extrapyramidal Symptoms Scale (DIEPSS)	• For assessment and screening of motor side effects of antipsychotic treatment • Eight symptom items and one global item • Optimized for newer antipsychotic drugs • Covers broad range of symptoms	Inada T: DIEPSS: A second-generation rating scale for antipsychotic-induced extrapyramidal symptoms: Drug-induced Extrapyramidal Symptoms Scale. Seiwa Shoten Publishers, Inc, Tokyo, Sep 17, 2009. (ISBN978-4-7911-0722-3)	Contact the author directly; toshiya.inada@gmail.com

39.2.1. Example of a Broad Symptom Assessment—Positive and Negative Syndrome Scale (PANSS) (Kay, Opler, and Fizbein, 1987) (4)

The PANSS was originally conceived to help overcome the limitations of older measures, such as the Brief Psychiatric Rating Scale (BPRS) and better capture and quantify a broad array of symptoms found in patients with psychotic disorders. Developed by Overall and Goreham in the 1960s, the BPRS was widely used for evaluating treatment efficacy of first generation antipsychotics (65). It had several advantages, including relative brevity, ease of use, and general applicability across inpatient settings. However, as novel treatments began to emerge with the development of clozapine and other second generation and atypical antipsychotics, some researchers began to appreciate the role of negative symptoms and other domains of pathology. The PANSS was developed, in part, to help overcome these limitations. At the present time, it is the most widely used assessment for patients with schizophrenia to evaluate treatment efficacy and is the primary outcome measure used in studies of antipsychotic medications. The PANSS has three subscales including a seven-item positive, a seven-item negative, and a sixteen item general psychopathology subscale for a total of thirty items. The scale is administered via a semi-structured clinical interview (PANSS) that takes approximately thirty minutes to complete. Data obtained from the interview is combined with additional information about the patient's symptoms and functioning over the past week and then used to help guide the clinician to score each of the thirty items.

The PANSS total score is computed by taking the sum of all thirty items. When administered on a regular basis, the PANSS is an excellent tool for tracking overall changes in symptom severity. Different combinations of items can be evaluated to focus on different aspects of pathology, guide treatment decisions, and help communicate information about patient progress among treatment teams. A subset of PANSS items and an abbreviated interview can be used independently from the larger scale to assess remission status. For further information about the PANSS and to obtain training, go to www.panss.org or contact info@panss.org.

39.2.2. Example of a Domain Specific Assessment—Negative Symptom Assessment-Four Item Version (NSA-4) (Alphs et al., 2010) (5)

Negative symptoms represent a considerable challenge in schizophrenia therapeutics, at an individual patient and a public health level (6). The NSA is a research tool designed specifically to establish the presence and severity of negative symptoms. The 16-item version (NSA-16) is well-known to have excellent psychometric properties and is sensitive to change over time in patients with schizophrenia (7). Several features make it optimal as an outcome measure in clinical trials, including high inter-rater and test-retest reliability as well as high concurrent validity with similar instruments (8).

A recent adaptation of the NSA undertaken by the authors has produced a brief measure intended for use as a screening tool and for clinical practice. Four items selected from the 16-item version (restricted speech quantity, reduced emotion, reduced social drive, and reduced interests) were combined with a global rating item of negative symptoms based on the rater's overall impression. The resulting scale, the NSA-4 is highly comparable to the original 16-item version.

The NSA-4 has several key advantages for use as a clinical outcome assessment. There is a concerted need to measure and screen for prominent negative symptoms and obtain measurement of treatment effects. The NSA-4 is highly reliable with minimal training across a wide range of educational and disciplinary backgrounds (5). The brief nature of the NSA-4 make it practical for routine clinical use.

39.2.3. Example of a Side Effect Rating Scale—Diagnostic Interview for Extrapyramidal Signs and Symptoms (DIEPSS) (Inada et al., 2009) (9)

Drug side effects, particularly motor side effects may limit the tolerability of treatments and affect compliance. The major classes of extrapyramidal side effects, including drug-induced parkinsonism, akathisia, and dyskinesias were recognized early on as common side effects associated with neuroleptic use. In clinical trials, many studies still employ three scales developed initially for studies of first-generation antipsychotics, including the Abnormal Involuntary Movement Scale (AIMS), the Simpson-Angus Scale (SAS), and Barnes Akathisia Rating Scale (BARS) (66–68). While each of these measures is highly valid and useful for assessing the specific extrapyramidal symptom for which they are designed, utility in everyday practice and time of administration of three separate measures continues to present a challenge. In response to these limitations and to the development of second generation treatments, several new instruments were developed, including the Extrapyramidal Symptoms Rating Scale (ESRS) and the Drug-induced Extrapyramidal Symptoms Scale (DIEPSS). Developed by Toshiya Inada in 1994, the DIEPSS is a brief, sensitive measure used to evaluate the severity of extrapyramidal symptoms (EPS) observed in patients receiving atypical antipsychotic drugs (9). It is a simple scale consisting of eight

individual items and one global assessment. The individual items include gait, bradykinesia, sialorrhea, muscle rigidity, tremor, akathisia, dystonia and dyskinesia. The severity of each parameter is graded from 0 (normal) to 4 (severe), and each category has clearly defined anchor points. Due to its simplicity in addition to its use as a measure of EPS in clinical trials, it is also effective as a screening instrument to facilitate detection of early manifestations of EPS.

The DIEPSS is a sensitive and reliable scale that can detect subtle changes of the severity of antipsychotic-induced EPS. High inter-rater reliability has been demonstrated in the number of reliability studies using an established training program. It is widely used in clinical trials and has been helpful for characterizing drug-induced EPS associated with newly developed ("second generation") antipsychotic drugs; several studies have used the DIEPSS with comparatively older agents in the double-blind randomized controlled trials performed in Japan and other East Asian countries.

Given the now relatively low incidence of EPS in schizophrenic patients receiving second-generation antipsychotic drugs, EPS scales with many items may be considered too burdensome for clinical and research use. Unlike the so-called first-generation EPS scales developed many years ago and conceptualized with higher frequencies and severity of EPS associated with first-generation antipsychotics, the DIEPSS is a second-generation EPS scale; its simplicity and high reliability make it suitable for assessing the low incidence of EPS in the era of second-generation antipsychotics.

39.3. Rating Scales for Depression

Depression is a common condition which can interfere with a person's ability to work, sleep, study, eat, and enjoy once-pleasurable activities. The 12-month prevalence of major depressive disorder in adults is reported to be nearly 7% (10) (http://www.nimh.nih.gov/statistics/1mdd_adult.shtml) while approximately 30% of these cases (nearly 2% of the U.S. population) are classified as having a severe depression. There are many rating scales to assess depressive symptoms as well as screens to identify the depressive syndrome. As with most psychiatric rating scales, the formats of scales differ and include both self and observer-rated instruments. Briefer scales are easier to administer in typical practice settings but may be less specific. Individuals with medical comorbidity may appear to have depressive symptoms (such as apathy) without depression, although it is not uncommon for people with medical conditions to have both depression and significant medical illness. As with any rating scale, it is important to remember that standardized rating scales can never replace a comprehensive clinical interview. Examples of rating scales for depression include the following.

39.3.1. Patient Health Questionnaire-9 (PHQ-9)

The PHQ-9 is a self-rated version of the Primary Care Evaluation of Mental Disorders (PRIME-MD) instrument that broadly evaluates common mental disorders (11, 12). The PHQ-9 is based upon Diagnostic and Statistical Manual (DSM) criteria and is often used in primary care and general medical settings to screen for depression. Each item of the PHQ is scored on a 0-3 continuum (higher scores indicate greater severity). Total PHQ-9 scores of 5, 10, 15, and 20 represent mild, moderate, moderately severe, and severe depression, respectively. A 2-item version of the scale, the PHQ-2 is often used as a "pre-screen" for depression in which individuals who score positively in either of the two items of the PHQ-2 would then be administered the full PHQ-9.

39.3.2. Hamilton Depression Scale (HAMD)

The HAMD (Hamilton Rating Scale for Depression) is one of the most commonly used rating scales and is designed to measure the severity of depression (13). It consists of 17 to 21 items, many of which address the somatic symptoms of depression. The HAMD may be less useful in some sub-populations with comorbid medical illnesses such as elderly individuals. However, given the very wide use of the scale over the last several decades there are multiple previous reports that suggest average ranges of the HAMD in various types of clinical populations. An additional strength of the HAMD is its reliability in evaluating change over time. The HAMD has been widely used in depression clinical trials. Each HAMD item is scored by a clinician on a scale of either 0-4 or 0-2. The HAMD requires 20–30 minutes for completion.

39.3.3. Montgomery Asberg Depression Rating Scale (MADRS)

The MADRS (14), which is intended to assess depressive symptoms, is derived from the Comprehensive Psychopathological Rating Scale. The MADRS consists of 10 items rated on a scale of 0-6 by the patient and by a clinician. Unlike the HAMD, it does not emphasize somatic symptoms of depression. There appears to be relatively good correlation between MADRS

and HAM-D scores. Inter-rater reliability on the MADRS with different pairs of raters has been reported to be 0.89 to 0.97. Inter-rater reliability between raters of different disciplines (psychiatrist/nurse) has also been demonstrated to be good. The MADRS requires approximately 20 minutes for completion.

39.3.4. Beck Depression Inventory (BDI)

The BDI (Beck Depression Inventory) is a widely used self-rated scale that assesses the severity of depression (15, 16). It consists of 21 items which are rated on a continuum of 0-3. It includes 2 subscales, a cognitive-affective subscale and a somatic-performance subscale, rendering it valuable in measuring depression in patients who are elderly, medically ill, or have a history of substance abuse. The BDI requires 5–10 minutes for completion.

39.3.5. Hospital Anxiety and Depression (HADS)

The HADS is designed to screen for anxiety and depression in hospital settings (17, 18) although it is often used in outpatient or community-dwelling samples. Of its 14 items, 7 pertain to anxiety and 7 pertain to depression. Each item is scored by the patient on a scale of 0-3. The threshold scores are 8 for mild depression, 11 for moderate depression, and 15 for severe depression. The HADS is a brief assessment that can generally be scored in under 10 minutes.

39.3.6. Center for Epidemiologic Studies Depression Scale (CES-D)

The CES-D, a frequently used scale in the medical literature, measures depression in community-dwelling populations (19, 20). It consists of 20 items rated by the patient on a scale of 0-4. Though higher scores suggest increasing severity of depression, a score of 16 is often used to categorize the threshold for depression. The CES-D requires 5–10 minutes for completion.

39.4. Rating Scales in Bipolar Disorder

Scales may be used to screen for bipolar illness as well as to measure symptom severity (21, 22). Bipolar disorder always involves manic and depressive symptoms, and may also involve problems related to anxiety, sleep, and substance use. There are fewer rating scales specifically for bipolar disorder than for some other common psychiatric illnesses such as depression (23) and it is common practice to evaluate bipolar patients with a mania-specific instrument (like the Young Mania Rating Scale/YMRS) (24) as well as a depressive symptom scale developed originally for individuals with unipolar depression (like the Montgomery Asberg Rating Scale/MADRS) (14). As with most psychiatric rating scales, the bipolar disorder scales vary in their design, format, and usage. For example, they may be rated by the patient, a clinician, or a trained rater. While patient-rated scales are often easy to administer, their use depends on the individual's ability to read, understand and accurately assess his or her status. Low health literacy or poor insight into illness may impede ability to self-score items. Clinician-rated or trained rater-administered scales often allow multiple sources of information to be taken into account (such as information from family or staff), but good interviewing skills by the rater remain an essential component of the interview. Although a variety of scales may be used, the Young Mania Rating Scale (YMRS) is the most commonly cited bipolar-specific scale in the medical literature (23). Examples of bipolar disorder specific scales include the following:

39.4.1. Mood Disorder Questionnaire (MDQ)

The Mood Disorder Questionnaire (MDQ) was designed to screen for past symptoms of mania or hypomania (25). It consists of 13 "yes or no" items derived from DSM-IV criteria for bipolar disorder. More specifically, one question details the clustering of symptoms, and another question details the severity of symptoms. While scores may range from 0 to 13, a score of 7 or higher with evidence of symptom clustering and at least mild symptom severity suggests bipolar disorder. The MDQ is a brief screening instrument that generally takes no more than 5–10 minutes to administer.

39.4.2. Young Mania Rating Scale (YMRS)

The Young Mania Rating Scale (YMRS) measures bipolar manic symptom severity, treatment efficacy, and relapse/recurrence (24). As it was designed to incorporate the full range of symptoms and severity of bipolar disorder, it is considered the most frequently used instrument in mania clinical trials. The YMRS is an 11 item checklist administered by clinicians or

trained raters. As each item is ranked on a scale of 0-4 or 0-8, scores may range from 0 to 60. Mild symptom severity is suggested to correspond to an average total YMRS score of 20, moderate symptom severity to an average of 26, and severe symptoms to an average of 38. It must be noted that these are simply total score means and any one symptom (such as suicidal or aggressive behavior) is often more relevant to clinical status and need for treatment rather than total YMRS score. It should be noted that there are four "double-weighted" items (irritability, speech, thought content, and disruptive/aggressive behavior) which will tend to inflate total scores in very ill and uncooperative patients. The YMRS requires approximately 15–30 minutes for completion.

39.4.3. Mania Rating Scale (MRS)

The Mania Rating Scale (MRS) is used in bipolar clinical trials (26), though less frequently than the YMRS. It consists of 11 items with 2 subscales (the Manic Syndrome subscale and the Behavior and Ideation subscale) and 1 question addressing insight impairment. A score of 39 or greater indicates severe mania. The MRS requires 15 minutes for completion.

39.4.4. Bipolar Depression Rating Scale (BDRS)

The Bipolar Depression Rating Scale (BDRS) measures bipolar depressive symptoms, with particular attention to atypical and mixed symptoms of depression (27, 28). It is administered by clinicians and consists of 20 items rated on a scale of 0-3. The BDRS and its scoring manual may be obtained from the scale developer at www.bawonhealth.org.au/bdrs/. The scale requires 15 minutes for completion.

39.4.5. Bipolar Inventory of Symptoms Scale (BISS)

The Bipolar Inventory of Symptoms Scale (BISS) was intended to cover the full spectrum of symptoms observed in bipolar disorder (29, 30). Of its 44 items, 22 pertain to depression and 22 pertain to mania. The BDRS consists of semi-structured interview questions detailing symptoms over the past week. Ratings for each question are on a scale of 0–4 and may be based on reports from the patient, family members, and clinicians. An advantage of the BISS is that a single instrument rather than two separate scales (one for depressive symptoms and one for manic symptoms) is being used to assess symptom severity.

39.5. Rating Scales in Trauma-Related Disorders

Patients with post-traumatic stress disorder are known to present with a variety of symptoms, including re-experiencing, avoidance, and hyperarousal. Those who have experienced chronic interpersonal trauma may also present with symptoms of numbing, dissociation, affect dysregulation and/or somatization. This latter type, described by Herman and others as "Complex Post-Traumatic Stress Disorder" (31) or van der Kolk et al.'s Disorders of Extreme Stress Not Otherwise Specified (32) is characterized by disruptions in domains of affect regulation, attention and consciousness, self-identity, and interpersonal relationships . Symptom patterns within and between patients (with or without complex features) may exhibit significant variation over time.

Assessments focusing only on re-experiencing, avoidance, and hyperarousal, while appropriate for persons exposed to a discrete, time-limited traumatic event, may not adequately measure symptoms associated with complex features frequently seen in survivors of prolonged and repeated interpersonal trauma. In recent years, efforts have also been made to evaluate the effectiveness of existing PTSD treatments for patients with complex traumatic disorders (33, 34) and psychotherapeutic treatments have been developed for this population by several groups including Cloitre (35) and Fosha (36).

Clinician Administered Measures: Several interview-based measures have been developed for confirming the diagnosis and evaluating symptoms of posttraumatic stress disorder (PTSD), most notably the Clinician Administered PTSD scale (CAPS) (37) which is widely regarded as the "gold standard" for PTSD assessment. An alternative assessment, the Symptoms of Trauma Scale (SOTS) has been proposed and is described in the example below. Clinician administered scales allow integration of direct clinical observation and assessment from semi-structure interviews. While these instruments have some limitations (e.g. time to administer, availability of trained, reliable clinicians, etc.) they are regarded as essential to evaluation of treatment progress and to detection of clinically-meaningful change.

Self-Report Screening Measures: These tools are patient-completed questionnaires designed to provide a basis of evidence for the presence/absence of likely trauma-related disorders or identifying possible subtypes. One example of a self-report measure in this category is the Posttraumatic Stress Diagnostic Scale (PDS), developed by Foa et al. (38) which is a 49-item self-report instrument designed to aid in the diagnosis of Posttraumatic Stress Disorder (PTSD). Respondents rate 17 items assessing the frequency of posttraumatic stress symptoms on a scale of 0 to 3. The PDS has demonstrated good sensitivity and specificity, internal consistency and test-retest reliability, and concurrent and convergent validity.

Symptom-Specific Questionnaires: Certain symptoms may be more problematic for patients and can represent unique treatment challenges. One example is dissociation, a troubling symptom that may be subjectively distressing and stigmatizing for some patients. The Dissociative Experiences Scale (DES) (39) is a commonly used 28-item self-report questionnaire, developed to assess dissociation in normal and clinical populations. Respondents indicate the percentage of the time they experience particular dissociative phenomena on a scale of 0% to 100% of the time. The overall DES score is the mean of all individual item scores. A meta-analytic study of the DES revealed high internal consistency, good test-retest reliability, and excellent convergent and predictive validity (40).

39.5.1. Example of a Clinician-Administered Scale—Symptoms of Trauma Scale (SOTS) (Opler et al., 2006) (41)

The SOTS consists of two components: 1) a seven-point rating scale used to measure current severity of each of twelve symptoms shown to be associated with trauma, and 2) a companion semi-structured interview, the Structured Clinical Interview for the Symptoms of Trauma Scale (SCI-SOTS), used to obtain information about the presence or absence of these trauma symptoms during a defined time period (usually the past week). The interview takes 20–30 minutes to administer. The symptoms assessed by the SOTS include Re-experiencing, Hyperarousal, Affective Dysregulation, Impulsivity, Avoidance, Numbing, Attention/Consciousness/ Dissociation, Self-perception, Interpersonal Relations, Alterations in Sexual Relations/Behavior, Sustaining Beliefs, and Somatic Dysregulation. The rating scale provides anchoring points which describe the symptomatology required for establishing each possible rating. An accompanying manual provides detailed information about administration and scoring.

Each SOTS item is measured on a seven-point scale from 1 (Absent) through 7 (Extreme), such that the SOTS total score can theoretically range from 12 to 84; in practice, for patients with trauma histories a score of 30 is low, representing remission, while 70 is high, reflecting many disabling symptoms. For further information about the SOTS and to obtain training, go to www.panss.org or contact info@panss.org.

39.6. Rating Scales in Anxiety Disorders

Anxiety disorders may be complicated to diagnose and measure for a variety of reasons. First, comorbidity across conditions is very common with some disease-state presentations demonstrating very high prevalence rates of anxiety—particularly generalized anxiety disorder (GAD) with early reports of comorbidities exceeding 80% (42). While DSM-5 maintains many of the categories and criteria found in the DSM-III, DSM-III-R, and DSM-IV, removal of the multi-axial diagnostic system and inclusion of dimensional approaches to psychopathology are noteworthy. Finally, it is very common for anxiety disorders to demonstrate considerable variability over time with a patient, making it important to identify sub-threshold cases for evaluation and monitoring (43).

A 2005 review by Antony and Rowa (44) identifies a number of challenges to the use of anxiety rating scales. One major challenge is the fact that certain scales have relatively low predictive validity for individual anxious responses to environmental situations. Specific symptoms may be difficult to attribute to underlying anxiety; they illustrate the classic example of heart-rate elevation. Elevated heart rate is a highly reliable measure and is sensitive to change over time, but it is also highly non-specific, i.e. there are a wide variety of factors that can affect heart rate, many of which have little to do with anxiety.

The types of rating scales that are commonly used can be divided into three basic categories. First, general rating scales may be used to assess anxiety without being specific as to subtype. Next, subtype-specific scales are focused on capturing the presentation of anxiety within a particular class, e.g. phobias or social anxiety. Finally, rating scales that evaluate the degree of impairment or dysfunction are useful tools for capturing improvement or worsening in social or occupational domains in patients with anxiety disorders (45). Each of these categories can be further subtyped into clinician-rated or self-report; some scales, including the Leibowitz Social Anxiety Scale (46) have both clinician and self-report versions available (47). Table 39.2 illustrates selected rating scales for assessment of individuals with anxiety.

TABLE 39.2 Selected rating scales for anxiety.

Scale name and acronym	Type	Key features	Reference
Hamilton Rating Scale for Anxiety (HAM-A)	Clinician or trained rater	• 14-items • Developed for Anxiety • Incorporates physical symptoms • Most popular anxiety rating scale • Separate structured interview (SIGH-A)	Shear MK et al. Depress Anxiety. 2001;13:166–178
Liebowitz Social Anxiety Scale (LSAS)	Clinician or trained rater	• Specific for use with social anxiety disorder • Primary outcome for SAD clinical trials • International recommended thresholds for bipolar depression trials entry • Heavily influenced by physical symptoms	Heimberg RG et al. Psychol Med. 1999; 29:199–212
Sheehan Disability Scale (SDS)	Patient-rated	• Widely used self-report measure • Well-validated and intuitive, requiring minimal instruction • Demonstrated value for self-monitoring of impairment due to anxiety • Can be completed in 5 minutes	Sheehan et al. Int Clin Psychopharmacol. 1996; 11 Suppl 3:89–95

TABLE 39.3 Selected rating scales that may be helpful in clinical practice settings.

Name of scale and acronym	What the scale measures	Format	Time needed to complete scale
Patient Health Questionnaire (PHQ-2/ PHQ-9)	Screening tool for depression. Individuals who endorse any item on the PHQ-2 are generally asked to complete the PHQ-9	Self-rated	Under 2 minutes for PHQ-2 5–10 minutes for PHQ-9
Beck Depression Inventory (BDI)	Depressive Symptoms	Self-rated	5–10 minutes
CAGE Questionnaire	Screening tool for alcohol abuse	Self-rated	Under 5 minutes
Fagerstrom Test for Nicotine Dependence (FTND)	Nicotine dependence in cigarette smokers	Self-rated	Under 5 minutes
Mini-Mental State Examination (MMSE)	Cognitive functioning in adults	Clinician or trained-rater administered	10–20 minutes
Montreal Cognitive Assessment (MoCA)	Cognitive functioning in adults (especially mild neurocognitive impairment)	Clinician or trained-rater administered	10 minutes
World Health Organization. Disability Assessment Schedule 2.0 (WHODAS 2.0)	Disability in adults	Self-rated	15–20 minutes

39.6.1. Example of a Generalized Anxiety Disorder Clinician-Administered Scale–Hamilton Anxiety Rating Scale (Hamilton, 1959) (48)

The Hamilton Anxiety Rating Scale (often referred to as the "HAM-A") is a clinician-administered measure with a total of fourteen items. Initially developed for use in patients with moderate-severe to severe forms of anxiety, it is one of the most widely used measures for anxiety research and particularly for studies of GAD. Each HAM-A item is rated on a 5-point (0-4) scale. One important advance on the HAM-A is the development of a structured interview guide, the Structured Interview Guide for the HAM-A (SIGH-A) by Shear and colleagues. The SIGH-A offers a standardized method for querying patients, allowing the clinician to efficiently obtain all of the data required to score each HAM-A item. The interview also helps assure standardization of assessment within and between subjects, assuring comparable data and evaluation techniques (49). Contact Dr. Michael Otto (mwotto@bu.edu) for further information about the SIGH-A

39.7. Use of Rating Scales in Clinical Settings

Table 39.3 illustrates some commonly administered scales and their content focus that may be readily implemented in clinical settings. As most clinics or mental health practices do not have dedicated staff available to administer rater-scored scales, the use of self-rated instruments is generally preferred for the average practice setting. In cases where patients may have limited insight into their condition (such as in neurocognitive disorders) clinician-administered assessment may be required but in this case the questionnaire needs to be brief and able to fit within the time and resource constraints of the average clinical visit.

Screening tools for depression such as the PHQ-2 and PHQ-9 are commonly used in clinical (mainly primary care) settings and the PHQ-9 is often used to assess depressive symptoms over time (11, 12). The Beck Depression Inventory (BDI) is another commonly used depression self-rated tool (15, 16). Relevant comorbidity factors such as drug or alcohol use/abuse may be assessed in both primary and specialty medical care clinical settings. Examples of such tools include the CAGE Questionnaire (50) for alcohol abuse and the Fagerstrom Test for Nicotine Dependence (51).

The DSM-5 recommends that symptoms be assessed both generally and specifically (1). An "Assessment Measures" section in DSM-5 includes examples of a small number of standardized tools to evaluate cross-cutting symptoms for adults and children (1) with some specific standardized rating scales. In individuals with neurological disorders, brief office-based cognitive assessments such as the Mini Mental Status examination (MMSE) (52) and the Montreal Cognitive Assessment (MoCA) (53) can be used to evaluate neurocognitive functioning. These may help determine the need for external support with activities that require executive or other types of cognitive processing as well as determination of need for additional neurological or neuropsychological evaluations. The DSM- 5 includes the World Health Organization Disability Assessment Schedule 2.0 (WHODAS 2.0) (54) which has replaced use of the Global Assessment of Functioning (GAF) as a recommended rating of disability related to mental disorder. Other examples of measures and additional assessments can be found online on the DSM-5 website: www.psychiatry.org/dsm5.

39.8. Use of Rating Scales in Clinical Trials/Research

The use of rating scales in clinical research differs from clinical practice in several important respects; most notably, the focus is not on therapeutic improvement of an individual patient, but rather on objective assessment of improvement with the goal of evaluating an intervention or new drug. Clinicians engaged in research must employ non-therapeutic research rapport (55), particularly when conducting placebo-controlled studies. The goal of this approach is to minimize expectation bias, conditioning, and other factors that may confound outcome and contribute to placebo response (56). Placebo response has been strongly implicated in increasing rates of trial failure which continue to plague clinical development of new pharmacological treatments in psychiatry (57).

Failure in this context is defined as any trial wherein the active treatment does not perform significantly better than placebo. While there are many contributing factors, high statistical variance and low inter-rater reliability in psychiatry and neurology are particularly problematic, especially in the case of multi-center trials. A variety of techniques have come into regular use to evaluate the integrity and reliability of study data (58). One of the most important steps that must be taken in service of regulatory as well as scientific objectives is inter-rater reliability training. A number of standardized practices around training and certification have been adopted and are now essential for completion prior to the collection of study data in any planned clinical trial (59).

Several publications describe the general training process, outlining various aspects including the use and selection of videotaped patient assessments as tools to help establish reliability when used correctly (60). Muller and Dragiecevic (60) describe a training program on the Hamilton Depression Rating Scale, showing that by going through a series of three videotaped assessments, acceptable inter-rater coefficients of agreement (ICC=0.57–0.73) can be achieved by novice raters/evaluators. This same trend has been demonstrated with other measures and disease areas (61). The consensus in the literature and in practice is that standardized videotaped interviews should be considered an essential element in any training program. The most important limitation of this approach has to do with the role of interview and assessment technique, specifically that passive scoring of pre-recorded interviews represents a very different challenge than the conduct of a well-conducted clinical interview. Several publications review the role of good versus poor assessment technique in accurate detection of treatment effects (62). Additionally, they explore novel training modalities to help improve both interview technique, item scoring, and inter-rater reliability. Lipsitz and colleagues (62) review the utility of teleconference-based "applied training" in assessment of depression. They describe the "Rater Applied Performance Scale" (RAPS) as a systematic method for evaluating interview technique. They conclude that the RAPS and similar approaches may form the basis for a new approach to evaluation of rater skill and ability to differentiate drug effects from placebo. Kobak, Opler, and Engelhardt (63) explore the importance of combining online training and applied sessions involving mock interviews with active feedback from expert trainers on the PANSS. They demonstrated significant improvements in RAPS scores over the course of the training. They also report significant reductions in expert-novice differences on PANSS items assessed, going from 9 points to 0.16 points of difference between trainees and trainers following completion of the program.

39.9. Future Directions

The use of rating scales in clinical practice and in research standardizes approaches for diagnosis and assessment. As the preceding discussion demonstrates, there is a considerable body of literature on the many ways to use rating scales to measure a variety of important health domains. But much work still needs to be done to optimize use of rating scales in advancing practice and research. For example, use of the electronic health records (EHR) is becoming the norm in most practice settings. Standardized instruments can help in identifying individual or groups of individuals in order to quickly and efficiently deliver treatment that is appropriate for a given individual. The more standardization can be achieved, the easier it will be to compare individuals or groups of individuals and assess the relative quality of care and outcomes across care settings. In the United States, the Affordable Care Act was passed by Congress and then signed into law by the President on March 23, 2010 (http://www.hhs.gov/healthcare/rights/law/index.html). A main thrust of the Affordable Care Act is the intent to deliver higher quality care while reducing costs. Rating scales such as some of those discussed in this chapter could be a way to help measure quality and support cost or value comparisons of new methods of healthcare delivery that are likely to be developed and implemented in the new healthcare climate. Additional future directions include increasing reliance on self-rated measures to empower healthcare consumers, particularly given the fact that many EHR systems are accessible for patients to review their own records and monitor their own clinical status or progress.

The section on use of rating scales in clinical trials notes evolving methods of rater training, which may reduce placebo response and increase efficient resource use. An additional future direction is the need to refine existing scales or develop new rating scales for the increasingly globalized setting for clinical trials. The number of countries providing trial sites outside the U.S. has more than doubled in the period between 1995–2005, while the proportion of clinical trials conducted in the U.S. and Western Europe has decreased (64). Issues of scale translation, cultural accommodation of a legacy measure, and determining best or most reliable application in a variety of settings and formats are a priority area for stakeholders involved in drug development.

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40
Neuroimaging in Psychiatry

Patricia J. Pardo, Ph.D., Cheryl A. Olman, Ph.D., and José V. Pardo, Ph.D., M.D.

Abstract The tools of neuroimaging and neurophysiology have recently made significant advances. Each technique delivers unique insights into the medical basis of neuropsychiatric disease. For these tools to augment personalized medicine, multiple neuroimaging and neurophysiological techniques must further mature while incorporating genomic information. This chapter is provided to create a foundation for understanding the major methods of neuroimaging and neurophysiology.

Keywords Computed tomography (CT) • Diffusion tensor imaging (DTI) • Electroencephalography (EEG) • Functional magnetic resonance imaging (fMRI) • Magnetoencephalography (MEG) • Magnetic resonance spectroscopy (MRS) • Positron emission tomography (PET) • Single-photon emission computed tomography (SPECT)

40.1. Introduction

The tools of neuroimaging provide visualization of the "invisible" suffering of patients with psychiatric disorders. Although not diagnostic, these pictures depict neurobiological correlates of cognitive and affective dysfunction in psychiatric disease. The future of personalized medicine for these patients is illustrated by the detection of individual differences in cerebral glucose metabolism patterns across patients with mild cognitive impairment (MCI), a status that often precedes emergence of one of the dementias (1). In a related role, neuroimaging guides levels of inquiry that are more microscopic, as well as pharmaceutical development. Given the high signal-to-noise ratio of subtractive approaches in neuroimaging in the comparison of the dementias to normative brain function, the application of neuroimaging to the evaluation of dementia serves as the prototype for clinical applicability of neuroimaging.

Five key principles optimize the usefulness of neuroimaging research to psychiatry. First, a mainstay of psychiatric neuroimaging has always been to characterize the healthy brain initially to provide a reference for interpreting brain function in

P.J. Pardo, Ph.D. (✉)
Assistant Professor, Departments of Psychiatry and Psychology, University of Minnesota, Minneapolis, MN, USA
Brain Sciences Center, Minneapolis Veterans Affairs Medical Center, Minneapolis, MN, USA
e-mail: pjpardo@umn.edu
http://www.brainsciencescenter.org

C.A. Olman, Ph.D.
Associate Professor, Departments of Psychology and Radiology, Center for Magnetic Resonance Research, University of Minnesota, Minneapolis, MN, USA
e-mail: caolman@umn.edu
http://vision.psych.umn.edu

J.V. Pardo, Ph.D., M.D.
Professor, Department of Psychiatry, University of Minnesota School of Medicine, Minneapolis, MN, USA
Director, Cognitive Neuroimaging Unit, VA Medical Center, Minneapolis, MN, USA
e-mail: jvpardo@umn.edu
http://james.psych.umn.edu

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disease. One cannot interpret data regarding an illness without the corresponding context of health. Second, converging neurophysiological and neuroimaging paradigms are necessary to deduce the real function of a particular brain area or circuit. In any one paradigm, many areas will become active; thus, the neural computation(s) of a brain region or network cannot be defined by any one study. Third, data interpretation of a clinical study depends on excellent characterization and diagnosis. Put another way, "Your data is only as good as your sample". The fourth key principle is a correlate to the third. It is imperative to use the best tools available. Often, the ideal research approach is most definitively addressed by integrating data from multiple neuroimaging and neurophysiological techniques [(2); e.g., EEG and fMRI]. Data should guide theory, not the reverse. Just because a particular structure "should" be active in a new paradigm and another not, real data frequently does not confirm such expectations. A better approach is to consider the data with a broader mindset than whether or not a particular hypothesis was confirmed or not. Moreover, novel findings may turn out to be instructive in reformulating of theory. For example, the unplanned discovery that middle temporal/Visual Area 5 cortex, "rMT/V5," previously hypothesized to be responsive to only visual stimuli, was found to be activated also by a moving somatosensory stimulus (3). Presently, the polymodal nature of MT/V5 cortex has been widely replicated with multiple imaging methods.

Currently, with the important exception of ^{18}FDG-PET cerebral glucose scanning for the subtyping of dementia in an individual patient presenting with symptoms not consistent with classic known subtypes of dementias (see Fig. 40.1), the visualization of brain regions underlying behavior and emotion seldom impacts psychiatric care. Nevertheless, recent technological and informatics advances in imaging methods have created more opportunities to study symptoms and disease at the level of the individual patient or subject (4). For example, ^{18}FDG-PET cerebral glucose scanning for the subtyping of dementia in an individual patient presenting with symptoms can be warped to a standard brain space and compared with normative neuroimaging databases, voxel by voxel, to yield a three-dimensional (3-D) image of significant differences for that individual (5). This approach is already in use to differentiate subtypes of dementias and is being evaluated for feasibility to address other psychiatric questions, such as subtyping of all psychiatric disorders. Technological advances in instrumentation in neuroimaging and neurophysiological technologies have powered these fields to go beyond identifying differences in brain function between clinical groups, to also now provide meaningful information in measurements at the level of a single

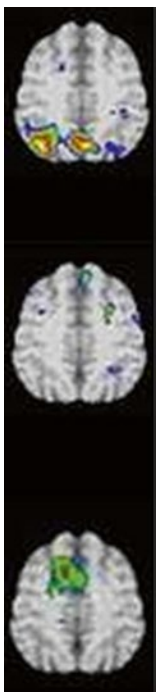

FIGURE 40.1. Following age regression, SVM based subtraction (horizontal orientation) images (of patient data from a psychiatrically screened relational PET ^{18}F-FDG database) shown at a horizontal digital slice of z = 40 mm (Talairach & Tournoux coordinates, 1988) for 3 different individuals, each diagnostically classified as having Minimal Cognitive Impairment, but exhibiting very different cerebral activation patterns at rest. These images follow the radiological convention of viewing the patient's brain from the foot of the patient's bed so the right side of the brain images appears on the left side of the brain image. Correspondingly, the left side of the brain images are shown on the viewer's right. This figure is adapted from Pardo et al. (1) Copyright (2010) with permission from Elsevier.

subject/patient (6, 7). As such, neuroimaging and neurophysiology techniques are increasingly being incorporated into clinical translational research. Future neuropsychiatric care will likely use high-end informatics to deliver personalized therapies by integrating a patient's clinical and family history of neuropsychiatric disease with key biomarkers derived from routine neurophysiological, neuroimaging, and genetic protocols. Moreover, such integration will also accelerate the development of more targeted therapies.

The goal of this chapter is to elucidate: 1) the basic methodologies for several major neurophysiological and neuroimaging techniques; 2) the methods applied to analyze these data; and 3) the relative strengths and limitations of these different techniques. We acknowledge that our coverage of these techniques is not exhaustive in the context of this diverse and rapidly evolving field of technologically driven systems neuroscience.

Given the cognitive and affective nature of psychiatric illness, the three fields discussed complement each as well as offer something unique to illuminate our understanding of neural systems in psychiatric illness. Neurophysiological methods such as EEG and MEG offer excellent temporal information, whereas neuroimaging methods offer excellent spatial information. Different tradeoffs between neuroimaging methods also exist. For example, fMRI does not involve radioactive isotopes, thus, it is a more benign tool for studying neurodevelopment. Yet, PET allows for straightforward whole-brain acquisition that includes ventral and medial structures, which are vital to understanding emotions. These technologies are highly complementary. For example, invasive neurophysiological recordings provide information regarding neuroimaging models. We argue that the complementary aspects of these fields should generate significant collaborative research. The infrastructure and personnel for employing techniques certainly can be financially costly, and combining them even more so. However, given the limited efficacy of current medical therapies for many patients suffering from psychiatric disease, the lack of diagnostic biomarkers for the affected cognitive and affective neural mechanisms impacted by psychiatric disease has frequently proven to be devastating for individuals and their families.

40.1.1. Introduction to Neurophysiology

EEG and MEG offer unmatched temporal resolution (<1 millisecond) of brain activity. Both are non-invasive, safe techniques that can reveal the timing of events occurring in large populations of neurons. They each measure synchronous postsynaptic activity (8–10), which corresponds well with the local field potentials obtained invasively in neural tissue (11). EEG and MEG methods continue to evolve to better localize the spatial coordinates of active brain regions ("neural sources"). Although much work has addressed the issue of source localization (spatial location in the brain) in EEG and MEG (E/MEG), scalp recordings still do not localize neural activity with the certainty of either fMRI or PET. In addition, deep signals that are weak may not be detected with E/MEG, and some electromagnetic signals may cancel each other at the level of the scalp. It is also conceivable that a very brief neural source might be detected by E/MEG and yet not detected by either fMRI or PET, as the latter techniques sum over longer time frames. Also, brief functional connectivity (i.e., the correlation in activity between different brain regions) between sources may or may not appear in fMRI or PET data. Thus, integrating across neuroimaging and neurophysiological techniques is essential to understand brain function in health and in psychiatric illness.

Although invasive intracranial recordings have direct spatial information, EEG and MEG do not. For this reason, localization from E/MEG data analysis must address the "forward problem" and the "inverse problem". The forward problem informs model parameters with the electromagnetic data from each sensor, 1) to first model the head as a conductor with one or more layers (e.g., brain, dura, skull, scalp; each having different electrical resistance properties), and 2) then to determine the electric potential or magnetic field distribution pattern in the head and on the scalp based on a model of activity in neural sources. Digitizing the locations of electrodes, position coils, anatomical fiducials (e.g., nasion, left and right periauricular tragus positions), and the scalp surface of each subject facilitates this process by creating a 3-D representation of the electrodes and scalp with respect to head/scalp coordinates, and, in the case of MEG, with respect to the superconducting quantum interference device (SQUID) channels used to measure magnetic flux. This information is then used to solve the forward problem. A structural MRI scan of the subject can improve the solution to the forward problem (12). The anatomical MRI scan provides shape and size information regarding the head and brain, as well as thickness of tissue layers. Thus, a realistic model of the head can be derived from segmenting the MRI into cerebrospinal fluid (CSF), scalp, dura, brain tissue, white matter, and grey matter and assigning appropriate conductivity values to each compartment.

The inverse problem involves relating observed data to a model of neural activity (i.e., given the data, predict the number and location of current neural sources, which may be modeled as dipolar sources). For E/MEG, addressing the inverse problem signifies a much more challenging task than addressing the forward problem. Just how accurate can E/MEG be in determining the exact number and locations of active neural regions? Although determining the scalp voltage or field topography generated by sources of known location and strength yields a unique solution, the inverse problem does not. Theoretically,

any one scalp topography determined using signals from the E/MEG channels could potentially arise from many different patterns of neural sources. A given scalp topography may result from 2 or 20 sources. Generally, the approach to determine the location and number of sources is parsimony: using as few as possible different sources to model the data unless external information specifies otherwise.

Other sources of external information come from fMRI, PET, or intracranial recordings. The extra source information may be from the subject performing the same task during an fMRI/PET study. In this case, fMRI/PET sources may be used: 1) to simply compare the presence and location of source modeling of fMRI/PET versus E/MEG modeling; 2) to place seeds in the E/MEG model to constrain the locations of active sources, using E/MEG primarily for its temporal information regarding active neural sources. When a subject's MEG information gets co-registered with the same subject's structural MRI, the fused data set is also referred to as magnetic source imaging (MSI).

The data may then be modeled by a variety of techniques (e.g., http://www.besa.de/; http://neuroimage.usc.edu/brainstorm; http://www.fil.ion.ucl.ac.uk/spm/; http://fieldtrip.fcdonders.nl/start; http://martinos.org/mne/stable/index.html#). The goodness-of-fit criterion of the E/MEG modeled sources explains the topography, as well as determines whether the neural sources are included in the solution. Other important methods addressing both the forward and inverse problems exist, but are beyond the scope of this chapter. Of note, waveform data, either transformed reference-free (EEG) or used directly from the sensor channels (e.g., MEG does not have a reference at another location, only a baseline in time), only display what was going on at the sensor level. Thus, these methods do not suffer from the inverse problem because no spatial predictions are made. Waveform data also embody the most primary (raw) form of the E/MEG data. Neurophysiological recordings may be performed at micro to macro levels. Such scale of measurement variations are reflected in the mere size of the sensors employed, which in the case of electrodes range from the intra-cortical nano-electrode, smaller in size than a red blood cell, to the more familiar scalp surface electrode used for EEG (see Fig. 40.2).

40.1.2. History and Data Acquisition Methods

40.1.2.1. Intracranial Neurophysiology

Electromagnetic stimulation of the human brain dates back to the days of Galvani. In 1803, John (Giovanni) Aldini observed positive mood changes in melancholic patients after electrical stimulation from a scalp electrode [for a detailed historical review of electrical stimulation research, see Boling et al. (13)]. Next followed the well-known animal studies by Gustav Fritsch, Eduard Hitzig, David Ferrier, and others' work in stimulating motor cortex (14). Although not the first to stimulate a patient's cortex during neurosurgery for epilepsy, Wilder Penfield and collaborators' electrical "probe" studies of awake patients extensively demonstrated this approach's usefulness in functional localization (15–17). Such electrical stimulation and recordings in humans and animals continue today. For example, evoking emotional states by stimulating the subgenual cingulate cortex can guide functional neurosurgery for treatment-resistant depression (18).

Today, dura and depth microelectrode recordings, although offering a small sampling of the available neural tissue in patients or animals (19, 20), still offer a "gold standard" perspective for both noninvasive electromagnetic recordings [EEG, MEG; (21)] and tomographic neuroimaging (PET, SPECT, fMRI). Present-day microelectrode studies use thin single channel or multichannel electrodes to sample across several layers of cortex or deeper structures. After the implanting of electrode grids or single electrodes with many points of contacts to localize the epileptic focus and neurosurgical target, patients may participate in cognitive or affective studies. Data may be presented as single or multiunit activity (MUA; thought to reflect the firing of action potentials) or current source density (CSD; derived from local field potentials). The spatial scale of intracranial recordings varies greatly across techniques (22, 23).

Although these research paradigms are often restricted to one brain region, these recordings continue to be invaluable in characterizing the spatial extent and overlap of localized functional areas, such as within the anterior cingulate cortex (24), as well as the heterogeneity of individual neuron's response to specific conditions. This information informs modeling and interpretation of neural activity studied at more macroscopic levels of inquiry, e.g., EEG, MEG, fMRI, or PET.

40.1.2.2. Electroencephalographic Instrumentation

Human EEG scalp surface recordings were first undertaken by the German neuropsychiatrist, Hans Berger, in 1929 (25, 26). The scalp EEG technique was based on Berger's earlier (1924) pioneering studies measuring electric potentials from the cortical surface of neurosurgical patients (27). The widespread and relatively economical technique of scalp EEG continues to augment our understanding of human affect, cognition, neurodevelopment, and sleep. Present-day research studies typically use from 21 electrodes (International 10-20 system) to 256 electrodes. Electrodes are customarily placed equidistant

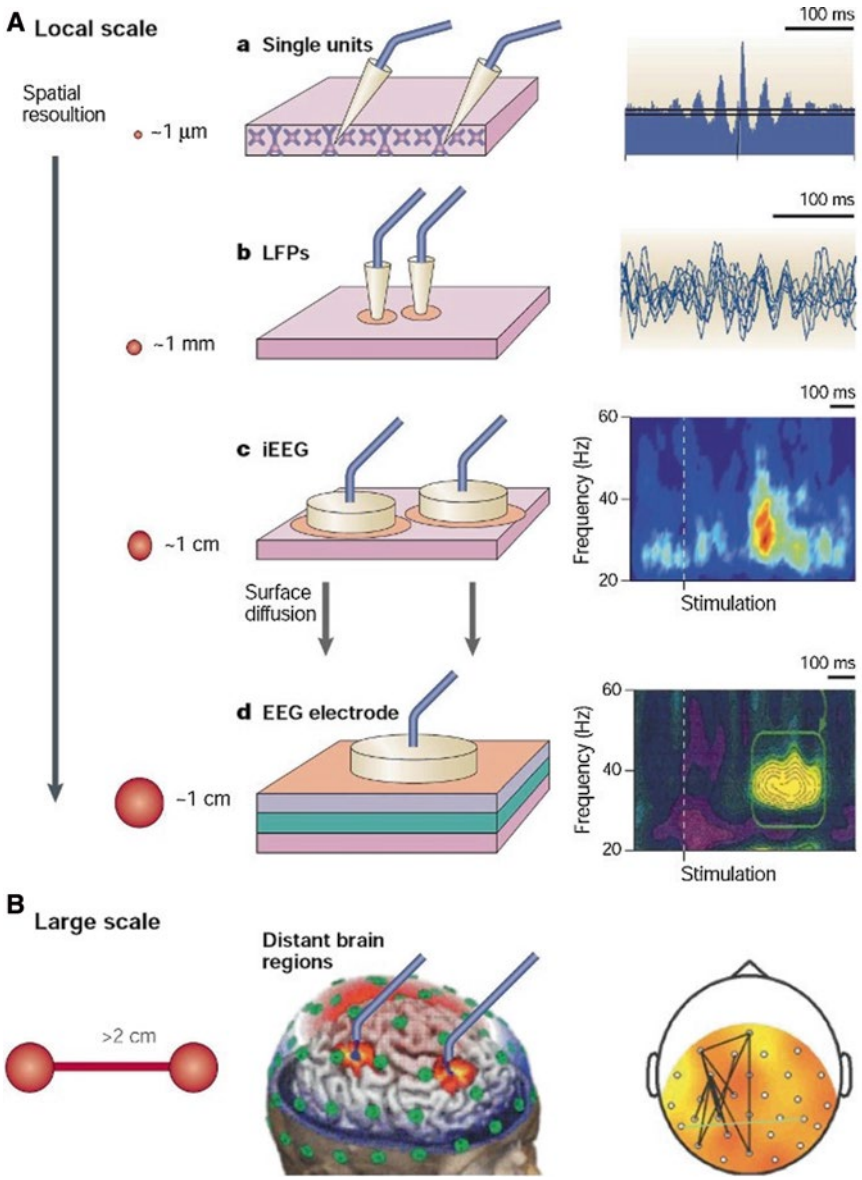

FIGURE 40.2. Neural synchrony as a multiscale phenomenon. A. Local scale: within a small brain region or local network, at least three levels of analysis can be distinguished. a) Synchrony between single units in monkey area V1 stimulated by a drifting grating, as measured by a cross-correlogram b) Local field potentials (LFPs) from eight recording electrodes in the suprasylvian gyrus of an awake cat. Maximum separation between electrodes was 7 mm. The overlapping traces show a brief episode of synchronization between the fast oscillations. c) Transient episodes of synchrony within a population of neurons recorded intracranially over the occipito-temporal junction in an epileptic patient performing a visual discrimination task. Time–frequency analysis revealed an enhancement of the local energy in the gamma band around 300 ms following the visual stimulation. This enhancement corresponds to the transient synchronization of underlying populations. d) When recorded from a surface electrode, such synchronous patches appear as spatial summation of cortical responses that give rise to transient increases in the gamma band. B. Large scale: patches of local synchrony in distant brain sites can enter into synchrony during cognitive tasks. Synchronous patterns between distant scalp electrodes were recorded in normal subjects engaged in a face recognition task. Black lines link electrodes that are synchronous during the perception of the face. (iEEG, intracortical electroencephalographic electrode; EEG, electroencephalography. Reprinted by permission from Macmillan Publishers Ltd. Nature Reviews Neuroscience (22) copyright (2001).

apart on the scalp and, frequently, the face. The standard naming convention include odd numbers referring to the left hemisphere; even numbers in the right hemisphere; and *z* in the middle of the head (28). Electrodes can be placed on the scalp individually, on an electrode cap, or in an electrode net, with polyethylene fibers between electrodes (29). Electrodes are typically made of silver and silver chloride, but may be coated with gold or placed in a tiny sponge covered in plastic.

Once the electrodes are in good contact with the scalp, usually accomplished with minimal skin abrasion and conducting gel, the subject has considerable mobility, offering the possibility of "real-world" research projects. For ambulatory recordings collodion paste adhesive may be used with traditional (nonsponge) electrodes to maintain the same level of resistance at each electrode site. Although some care must be taken to maintain good electrode contact with the scalp, this mobility is unique in comparison with fMRI, PET, and MEG methods. For instance, EEG recordings have even been made of pilots as they fly helicopters (30).

The signal from the electrodes goes to the EEG amplifiers, which may be shielded to increase SNR and for use in MEG or MRI environments. Next, the analog amplified signal is converted to a digital format for computer analyses (31). Using an electrically shielded room (a "Faraday cage") often made of wood and copper can improve SNR of EEG recordings. Recording EEG data in a realistic environment ensures generalizability of findings to that environment. However, SNR can be optimized in the EEG laboratory setting (31).

The recorded electrical potential is the difference in potential between two locations. Therefore, the choice of reference directly impacts voltage topography and channel wave-forms. EEG data can be processed after data collection into average reference ("reference-free") montage formats and derivations (e.g., Laplacian, Hjorth) or CSD (32, 33). The electrical resistance of the skull and scalp blur the signal measured by EEG, thus, realistic modeling of each subject's skull and scalp can "deblur" (34) the signal, providing spatial information of the active neural sources that is more accurate. Co-registration with one subject's anatomical MRI data to measure skull thickness and other parameters facilitates such modeling. Other strategies include applying a small charge to the scalp and measuring the potential (EEG) or magnetic flux (MEG) to model the impedance caused by the skull.

40.1.2.3. Magnetoencephalography Instrumentation

The first MEG measurements were achieved by David Cohen at the Massachusetts Institute of Technology (MIT) in 1968 (35). He collected data from his one channel instrument inside a MSR that isolated the weak brain neuromagnetic signal from the environmental magnetic noise (36). The inventions of the direct current (DC) SQUID by Robert Jaklevic, John Lambe, Arnold Silver, and James Mercereau in 1964; and the radio frequency (RF) SQUID by James Zimmerman and others in 1965, advanced development of this technique (37). Eventually, neuromagnetometer systems contained multiple MEG channels, permitting better spatial sampling of neuromagnetic activity.

Significant momentum for basic and clinical MEG research began when Antti Ahonen and fellow Finnish physicists developed the world's first whole-head neuromagnetometer. The helmet-shaped array (evocative of an old-fashioned salon hair dryer) could sample 122 channels simultaneously (38). Whole-head MEG systems now have 148 to over 500 channels (individual sensors). The cost of buying the MEG instrument and MSR (see below) contribute to the significant MEG startup expense. This expense has negatively impacted the availability of MEG, even in major medical centers. However, most recently FDA approved procedures for clinical use of MEG in epileptic patients that will be undergoing neurosurgery, have led to several recently opened MEG centers. The data flow paradigm for MEG mirrors EEG, in that MEG data is detected, amplified, converted from analog to digital, and transferred to computers for further processing. For clinical application of MEG to presurgical mapping for epileptic patients, MEG is employed to detect active epileptic seizure foci and to detect the function of neighboring areas of the brain to predict functional outcomes post-surgery.

Magnetic sensors (magnetometer or gradiometer), detect changes in neuromagnetic flux coming from the brain. Each type has a superconducting pick-up coil (flux transformer) in either liquid helium or liquid helium-cooled space that is near absolute zero (~4 K). This pickup coil is coupled to a DC SQUID by the input coil (39). The DC SQUID loop and input coil are immersed in liquid helium (or helium-cooled space) to allow superconduction to occur over two weak links, called Josepheson junctions (40). It is here that the magnetic flux emanating from the head is detected, and, with the help of feedback electronics, the SQUID functions as a flux-to-voltage converter. High-temperature SQUIDs systems are under development, but, currently, are not as sensitive as low-temperature ones.

There are three major types of pickup coils: magnetometer, first-order planar gradiometer, and first-order axial gradiometer. The single loop magnetometer pick-up coil is the most sensitive of the three in detecting neuromagnetic flux. However, it is also the most sensitive to unwanted environmental magnetic noise. This large amount of noise is customarily addressed at the software level. The other two types are first-order gradiometers. The planar first-order dual gradiometer pick-up coil uses two thin-film rectangular loops on the same square silicon chip, parallel to the surface of the dewar, which, in turn, is roughly parallel to the surface of the head. The magnetic flux gradient between the two loops is the signal detected. The pair of planar gradiometers on the same chip is orthogonal to one another, and each detects different orthogonal tangential derivatives (gradients) of flux.

To understand the orthogonal relationship between the two figure eights in a sensor pair, it may be helpful to picture the head as a sphere, with one of the figure eight gradiometers detecting derivatives of flux along a latitude dimension and the other in the pair detecting signal, but along a longitudinal dimension. The other common pick-up coil is the axial

gradiometer. The axial gradiometer is located approximately normal to the head's surface. The flux detected by the lower loop is directly compared with the signal from the upper loop. The upper loop, farther from the brain, should, in principle, detect primarily environmental, non-brain noise. Thus, the flux in the upper loop (from environmental noise and brain activity) gets subtracted from that of the lower loop (mostly brain activity) to extract the neuronal signal. Unfortunately, gradiometers of any kind likely throw out some of the brain signal (baby) with the noise (bath water). However, because of its conservative design, detection of flux with a gradiometer is likely to be neural in origin. For these reasons, these "near-sighted" gradiometers are particularly well suited for studying the cortex.

Magnetically shielded rooms (MSRs) and magnetometer shields contain nonferrous materials, such as aluminum and mu metal (an alloy of five metals), to shield out high- and low-frequency noise, respectively. Some MSRs also use active electrical shielding (41) to further shield the weak brain signal (10–15 to $10-12$ T) from the earth's magnetic field ($10-5$ T) and from other sources of unwanted magnetic contamination (lights, elevators, traffic, etc.). The spectral frequency of these noise sources overlaps completely with that of the brain. Thus, much effort is expended to eliminate any magnetic noise during an MEG study. An example of this is the development of nonmagnetic stimulators (plastic tubes for sound delivery, air pressure vibrators for tactile stimulation, etc.) and nonmetallic response boxes.

The MEG subject, seated or supine, must remain very still during the study, which may be brief (40 seconds) or lengthy (1 hour). Because the neuromagnetic signal drops off with the square of distance from the channels ($1/r^2$), infants may be measured with more sensitivity by resting the head on one side of the helmet-shaped opening. Recently, to address the issue of head size and the related issue of signal drop-off with children, a few smaller custom neuromagnetometers have been made to facilitate sensitive whole-head recordings of infants and children. Even neuromagnetometer systems with special dewar shapes are available for MEG in utero. The dewar is a cryostat that functions as an insulated thermos to contain liquid helium, which, as mentioned above, permits cooling to super-conducting temperatures. Because no dewar is perfectly insulated, refilling the dewar with helium represents one of routine and unavoidable expenses in operating an MEG facility.

Unlike scalp electrical potential measurements, the neuromagnetic flux in MEG measurements has been shown, with animal studies, to remain not blurred by the skull and scalp (42). This transparency of the skull, scalp, and intervening tissues to the MEG signal results in superior spatial information than EEG.

Because of the physics of picking up magnetic flux from a coil parallel to the scalp surface, MEG technology inherently is biased toward tangentially oriented neural sources, such as those occurring in sulci. MEG may not even detect radially oriented sources, such as those located on the top of a gyrus that is perfectly radial to the scalp. Hildebrand and Barnes (2002) estimate that a 2-mm strip of cortex on the crest of a gyrus is poorly detected with MEG (43). On the other hand, EEG technology can detect sources of any orientation. This complementary nature of MEG and EEG has led to simultaneous MEG and EEG recordings (44, 45). All major manufacturers of MEG include EEG integrated into the design. The main reason MEG studies do not always record EEG simultaneously is of a practical nature. Combined recordings mean longer time spent in subject preparation. In addition, even low-profile electrodes take up appreciable room in the MEG helmet, thus, may result in too tight a fit for some subjects with larger heads. This problem arises from MEG whole-head systems typically designed to accommodate the head size of only 98% of local populations. This design strategy maximizes signal detection by minimizing the distance from the brain to the sensors at the expense of limiting usefulness to specific head sizes and shapes. Of course, if practice effects are not a concern, the MEG and EEG measurements can be done in separate study sessions. In addition, recording from one or two EEG electrodes during an MEG study takes minimal preparation time and very little space in the helmet-shaped dewar. This approach can be helpful in detecting neural currents radially oriented to the skull (e.g., the peak of a gyrus), poorly detected by the MEG sensors, or to compare waveform response from EEG.

Often, the waveform responses from MEG and EEG look somewhat similar (46). Differences likely arise from MEG's tangential property (blind to perfectly radial sources) and from EEG's being blurred by the skull. Thus, a comparable EEG waveform may contain electrical potential information from more neural sources than does the MEG waveform. For this reason, MEG waveform deflections are termed differently than those used in EEG. For example, the corresponding MEG event to an N100 in an evoked EEG paradigm is often termed either N100m or M100.

Technological improvements continue on many fronts. Recent hardware improvements include less noisy SQUIDs and the placement of reference channels in the dewar to detect environmental noise. Current software modeling of magnetic noise aids in modeling and subtracting unwanted magnetic noise from neural flux data. High-performance computing now routinely provides functional connectivity across different brain regions during a task.

40.1.3. The E/MEG Signal Origin and Spontaneous Oscillations

Intracranial microelectrode recordings typically measure: 1) rapid spike action potential activity from individual neurons; or 2) more slowly occurring changes in the local field signal that is generated extracellularly by one or more neurons. The local field signal is hypothesized to reflect more slowly occurring integrative activity in the dendrites (47). The post-synaptic

neural activity measured by either MEG or EEG reflects synchronous local field activity at a population level; thus, it is most analogous to extracellular recordings. MEG and EEG arise from the same current source. A corresponding magnetic field is generated with every electrical current source, following the "right hand" rule of physics, with the thumb representing the direction of electric current and the curled fingers the direction of the magnetic flux. Most activity recorded from either technique arises from extracellular, postsynaptic events in pyramidal cell neurons, the most common type of neuron in the cortex (47). Cortical layer 5 is considered to contribute heavily to recorded EEG potentials or MEG fields. Layer 3 also contributes to a smaller degree.

The cycling speed or frequency of the E/MEG signal varies from 0.01 to 1,000 Hz. In addition to evoked activity, ongoing oscillations containing prominent "signature" frequencies can be recorded at particular areas of the cortex. Hans Berger was first to characterize the alpha "band" of 8- to 12-Hz spontaneous oscillations over occipital areas. The names of frequency bands denote both the frequency of the oscillation as well as their location. For example, the mu band has a frequency range that overlaps considerably in frequency with that of the occipital alpha band, but mu is recorded over primary somatosensory and motor cortex. The oscillations occurring in the absence of a sensory stimulus or task are termed spontaneous oscillations.

Commonly known bands and their signature frequency ranges include delta (1.5–6 Hz), theta (6.5–8 Hz), alpha (8.5–12 Hz), beta (12.5–30 Hz), gamma (30.5–80 Hz) and ultrafast (>80 Hz). The spectral composition of spontaneous oscillations is typically obtained with fast Fourier transforms from wide bandwidth (e.g., 0.01–400 Hz) data (22). Time-frequency plots of elicited or spontaneous oscillations can be analyzed by several methods, including wavelets and other time-frequency transforms (48, 49). For years, scientists have speculated on the origin and role of these synchronizing frequencies. Some view these spontaneous oscillations as "idling" rhythms (50, 51) akin to keeping the engine warm or ready to go. Others hypothesize that oscillations serve to bind the distributed neural networks that make up the substrate of mental representations (52, 53). Thalamic contributions to these cortical rhythms have been demonstrated in animal studies (54, 55). The amplitude of the spontaneous oscillations is several times greater as compared to that elicited from evoked responses (5–100 versus 10–15 fT) described below.

Frequently detected waveform patterns elicited at certain times and under conditions have components with named waveforms. These waveforms occur often in the context of an experimental trial, thus, are part of the event-related potential (ERP) or event-related field (ERF) for EEG and MEG recordings, respectively. For example, the P50 habituation phenomena involve a positive EEG deflection or corresponding MEG deflection (termed P50m or M50) occurring approximately 50 ms after the start of the second 3-ms auditory click. Schizophrenic patients often exhibit less habituation to the second click (56). The P or N part of the component name refers to the polarity of the electric potential signal. As illustrated above, an MEG channel does not require a reference channel. MEG components may be denoted with M (e.g., M50) or may be named for their corresponding electrical component, but designated as the magnetic (e.g., P50m) aspect of the component. Many other named components exist, but are beyond the scope of this chapter. For a thorough description of elicited waveform components, please see pp 34–50 of Luck (31). Evoked responses for either MEG or EEG are elicited synchronously and are in the same phase for each trial. Induced responses are those elicited synchronously, but not so synchronous as to be at the same phase for each trial.

40.1.4. Data Analysis Methods for EEG and MEG

40.1.4.1. Addressing Noise in the Signal

The subject inherently brings electromagnetic noise to each E/MEG study. Eye-blink, cardiac, respiratory, and muscle artifacts can significantly influence the quality of the data acquired. To detect and/or characterize common sources of non-brain noise, electro-ocular and electrocardiac electrodes are often included in E/MEG setup. The purpose of collecting these data is to detect instances of eye-blinks or to characterize noise from the heart. Data collected during blink artifacts are often simply eliminated from further data analysis. One just needs to collect more trials during a study to allow for some loss of data. For some purposes, such as longer trials or time series analyses (with the eyes open), this approach is not feasible. One then models the eye blink noise and removes it from the data (often done using independent components analysis). However, because the eye blink noise is so strong compared with brain signals and because modeling is never perfect, when feasible, it may be best to simply eliminate noisy trials, if possible. Also, the eye blink event itself has its own pattern of neural activity (57, 58).

One of the most insidious sources of magnetic noise is the heart. Thus, for MEG, the cardiac signature is often modeled using lower MEG channels and/or the ECG; it is subsequently removed from the E/MEG data. Cardiac electrical noise can also be modeled and removed from E/MEG data (59). This step is particularly important when studying single trials with either MEG or EEG. Another strategy to address this concern averages more than 70 trials for every condition so the cardiac and respiratory signals are eliminated (60).

Muscle artifacts can also obscure brain data. For example, tense neck muscles may taint an E/MEG recording of evoked responses in the brain stem. Therefore, subjects are encouraged to relax their muscles. Subject movement artifacts are more troublesome for MEG than EEG due to MEG's sensors being in fixed locations in relation to the subject's head. Data acquired during the time of the movement can be unusable. This, of course, affects the feasibility of studying agitated patients. Devices such as pillows, foam helmet inserts, vacuum pillows, and inflatable, circular tubes supporting the head and neck aid the subject's comfort and encourage immobility. Some MEG systems use the head placement coils to detect movement every few milliseconds and later correct the data for movement (61, 62).

Environmental electromagnetic noise is pandemic. Some metal orthodontic appliances, such as braces or built in retainers, introduce large amounts of unwanted magnetic noise. Even some hair dyes and mascara can introduce significant magnetic noise. Electrical power lines, the earth's magnetic field, elevators, and subways are other sources of unwanted magnetic flux, thus, the exact site of the shielded room impacts the quality of E/MEG recordings.

40.1.4.2. Phase-Locked, E/MEG Evoked Responses

Phase-locked, evoked brain responses are elicited responses that are largely reproducible across single trials. Often these trials are averaged for each E/MEG channel by condition, resulting in a waveform that is smaller and smoother (possessing fewer higher frequencies) than that from any single trial. The difference between an averaged response and a single trial response arises from the variation across the single responses from the brain and the jitter in noise sources (e.g., cardiac artifact) across trials.

When many response trials are averaged, the waveforms of noise in each trial are averaged as well. If there are a sufficient number of trials per condition (e.g., 100 trials per condition), these noise waveforms typically cancel one another during the trial averaging process since they are usually not time-locked to any aspect of the trial. Some variations in neural responses of interest may also be cancelled in the averaging process so other methods may be employed to address the presence of noise in the data. The term methods may be empiric to the average response across conditions for one subject or the average response in one condition across multiple subjects. The trials are typically determined by the onset of a stimulus, but may also be the onset of a response time or the onset of a neural response that is based on a template (derived iteratively from averaged responses). Typically, the significant differences in single trial responses across individual subjects result in very smooth waveforms for grand averages across subjects. The coupling of brain areas with responses evoked at the same time or at a consistent lag can be studied with time series analyses of different channels (63). This strategy addresses the functional connectivity in brain responses at the millisecond level.

Analysis of evoked E/MEG data proceeds at the sensor level or brain level. Sensor-level data come from single trials or averaged trials. An evoked response is often modeled with an equivalent current dipole (ECD). The ECD's location and strength are determined by iterative least-squares algorithms. The ECD, also called simply a "dipole," has no volume, only location and orientation. Modeled dipoles usually meet the criterion of 90% or greater goodness of fit, thus, noise is not part of the modeled neural data. Usually, most elicited responses are also composed of "induced" responses, not as phase-locked to the response (see Sect. 40.1.4.3).

40.1.4.3. Out-of-Phase E/MEG Part of the Model

Induced E/MEG responses are elicited just as in evoked responses, but they are termed "induced" to denote inconsistency of phase information across trials. "Induced" responses contain event-related synchronization (ERS) and event-related desynchronization (ERD). Occurring in parallel across a trial, certain oscillation frequencies can become more active than at baseline (ERS), and others less so (ERD). ERS/ERD detection often requires large groups of channels and usually requires significant time (seconds) to rebound to the level of spontaneous oscillations. In some paradigms, a center surround pattern emerges, with central channels displaying ERD and more distal channels displaying ERS (64). One method of studying ERD/ERS uses temporal spectral evolution (TSE) (65). The signal of each trial gets rectified (taking the absolute value of the waveform at every point before averaging across trials). Changes in ERD/EDS stand out the most if the length of the intertrial interval approaches several seconds. This allows for the spontaneous oscillations to return to baseline levels. The examples below illustrate data analysis strategies for both types of elicited responses.

40.1.4.4. Advanced E/MEG Data Analyses

There are many different methods to analyze E/MEG data. In contrast to the dipole model above, which does not specify the volume of activated tissue, data analyses can use more extended/distributed models. The distributed models have different assumptions. Thus, the same data modeled previously with ECDs identifying location, strength, and direction of point

sources in the brain will look more blurred and extended over a spatial region—unlike a point source—when analyzed with a more distributed model. Again, *it is still the same data*, *whether modeled as tiny points or large brain areas*. Intracranial responses often identify a large area of neurons participating in a task, [(e.g., language (66)]. Accordingly, the distributed models are probably closer to reality. Just how the boundaries of active areas are defined is an active area of computational research. Two common models of the brain as a conductor are the "L1" and "L2," "lead fields" (40).

Active sources typically have more volume in L2 models than in L1 models. Some models result in more cortical activations, and others accommodate subcortical activation. On the other hand, the dipole model makes no claim regarding the extent of an activation, so will never make inappropriate estimates of activated volumes. Also, not all responses are dipolar, such as induced responses, so ECD models do not include non-dipolar activity.

Noise or large neural sources are sometimes "removed" from the data through signal space projection methods (67) thereby permitting the modeling of weaker sources. Beamformer data analyses model noise and project the neural sources (averaged over small time windows, such as 25 ms) with narrow frequency bandpasses (e.g., 8–15 Hz) to different brain regions. These methods demonstrate that neural activity in one narrow band may be located in entirely different brain regions than those of another narrow frequency range. The images of the beamformer sources look a lot like the images generated by fMRI blood oxygenation level-dependent (BOLD) or ^{15}O PET (68) techniques. Originally, all neural sources with beamformers were modeled as uncorrelated with one another (69), but this approach now has many variants, with one permitting correlation of neural sources (70). Some source analysis methods, such as the Minimum Norm Estimate (71) or Minimum Current Estimate (72), constrain source location largely to the cortex, but these methods also have variants, such as the depth-weighted Minimum Norm Estimate (73). Other data analysis approaches include more Bayesian methods. The plethora of analysis approaches can easily overwhelm the reader. The main aspects of analyses are the following: sensor level versus neural source level; point versus distributed; region versus connectivity; evoked versus induced versus spontaneous; constrained (by previous information or model) versus unconstrained; and choice of the conductor shape for the brain (e.g., sphere, generic realistic head shape, MRI-generated conductor shape with tissue boundaries). As with tomographic neuroimaging, neurophysiological analyses often include measuring functional connectivity across multiple brain regions. E/MEG connectivity analyses exploit E/MEG analyses ductor shape to detect in the context of a specified task and the temporal order of activated brain regions. Since E/MEG directly measures neural activity, not a distal marker of neural activity, it offers a much greater temporal resolution of brain activity than is possible with MRI or PET neuroimaging techniques. Full analyses of this rich information of time-related connectivity may require the use of high performance computational software.

40.1.5. Applications. What Can We Learn from Neurophysiology?

As mentioned above, invasive intracranial recordings directly measure the spatiotemporal nature of activity in samples of individual neurons or small groups of neurons. Very thin microelectrodes placed as grid or multichannel units in animal subjects or neurosurgical patients can reveal neural behavior to sensory stimuli, emotion induction, attention, language, or task behavior. Non-invasive E/MEG reveals the "when" (timing) and, in many cases, such as the cortex, the "where" of active populations of neurons. Simultaneous MEG and EEG optimally characterize ongoing brain signals, as the two methods measure the same type of brain signal, with each technique offering both overlapping and unique information. MEG optimally detects tangential neural activity, and its signal is not blurred by any tissues. For these reasons, MEG is an excellent choice for measuring cortical responses within the cortical sulci. EEG detects both radial and tangential oriented brain activity, but its signal is blurred by the skull. A few examples of topics that have been investigated with neurophysiology follow.

40.1.5.1. Neurodevelopment

The safety of E/MEG facilitates studies of development of neural capacities such as sensory processing, attention, learning, language, arithmetic, and motor control. For example, Lauronen et al.'s MEG study of tactile processing in healthy newborn infants versus adults evoked very different waveform responses to electrical median nerve stimulation (74). In a study of arithmetic tested using videotaped presentations of puppets, Berger et al. (75) found analogous patterns of evoked EEG responses to correct and incorrect arithmetic solutions in adults and 6- to 9-month-old infants, suggesting that such infants have some aspects of numerosity (75). Rojas's MEG study of auditory processing in children and adults illustrates the dynamic nature of the brain's auditory response (76). Differences in EEG topography related to the processing of errors are more evident between adults and adolescents with increased task difficulty (77). Aine et al. (2006) found different patterns of neuromagnetic responses in six brain regions for young and elderly adults preforming memory tasks (78).

40.1.5.2. Perception and Cognition

Neurophysiological recordings can aid in understanding information processing. An MEG study of pain by Forss et al. (2005) detailed different time courses for neural correlates of pain information carried by two different pain fiber pathways (79). Intracranial recordings of human ventral occipitotemporal cortex by Allison et al. (1999) identified a larger patch of cortex responsive to face stimuli in the right hemisphere versus the left for the N200 response (80). This result is congruent with findings in neurological patients with proposagnosia showing right greater than left effects of hemispheric lesions in ventral occipital cortex.

E/MEG measurements also have been useful in understanding information processing in psychiatric illness. Reduced P300/P300m evoked responses to the onset of target stimuli (81) and reduced N400/N400m (82, 83) responses to unexpected endings in sentences have repeatedly been found in schizophrenia and other disorders. MEG studies of evoked sensory responses have found altered hemispheric asymmetry in schizophrenia (84). Different profiles of neural oscillations evoked by speech sound were found across healthy subjects and patients with either schizophrenia or bipolar disorder (85).

40.1.5.3. Emotion

Intracranial stimulation and E/MEG studies offer vantage into the neural circuitry of emotion. Meletti et al. (2006) found sex differences in frequency of emotional responses (e.g., fearful, sad, happy) to temporal lobe stimulation (86). In men, only 3% of the stimulations resulted in a change in emotional state, as compared with 16% for women. Using pictorial stimuli of faces depicting various emotions, Parker et al. (2005) measured dramatic reductions in evoked potential responses in young children (7 to 32 months of age) who had been institutionalized at very young ages as compared with never-institutionalized children of the same age (87). However, in adults, increased range in ERP to socially positive (grade of an A) versus socially negative (grade of an F) feedback was found in depressed patients as compared with control subjects.

40.1.6. Integrative Applications

Combining different techniques and methods in studies of the same subjects and patients has often led to noteworthy discoveries. Such approaches often involve the efforts of cross-disciplinary collaborations so these studies may be more costly. Nevertheless, as revealed in the following subdivisions, these integrative approaches yield important, unique insights.

40.1.6.1. Neurophysiology and Neuroimaging

Connecting E/MEG neurophysiological data with fMRI/PET data can validate or constrain the source modeling of E/MEG and provide a fine-grain temporal profile of neural responses. In Bar et al. (2006), fMRI neuroimaging provided the constraint on source location to enable modeling of the time course of MEG neurophysiological responses in orbital frontal cortex [OFC; (88)]. The fMRI BOLD and MEG acquisitions were done separately, using the same paradigm to study object recognition. This combination of techniques allowed for confident source localization in the OFC from modeling of MEG data. This area is difficult to assay with MEG alone because OFC is located behind the eyes, which is a common and large source of artifact for E/MEG.

Of course, simultaneous acquisition of neurophysiological and neuroimaging data is the best design. In a study by Nofzinger et al. (89) combining EEG and ^{18}FDG PET scans, neurophysiological data from study subjects was acquired from defined sleep stages. From the waking state to rapid eye movement sleep, depressed patients showed increases in relative metabolism in the reticular formation and in anterior paralimbic cortex. Specially designed electrodes and caps have facilitated simultaneous EEG and fMRI BOLD acquisitions. Simultaneous acquisition of ERP and fMRI BOLD during object motion in a study by Wang et al. (1999) revealed parallel time courses of activation in ventral and dorsal visual pathways (90). Of note, care in interpretation becomes important, since when one signal increases, such as BOLD, another signal, such as alpha frequency, may decrease (91).

40.1.6.2. Combining E/MEG with Genotype

Increasing knowledge regarding the role of genetic polymorphisms in the phenotypic aspects of behavior, personality, and psychiatric disorders prompts new interest in combining genetic and neurophysiological information (92). In an ERP study, Johnson et al. (1997) found the amplitude P300 waveform component (hypothesized to reflect attentional and working memory resources) depended in part on the specific polymorphism of the cannabinoid receptor gene (93). Using MEG,

Cañive et al. (2006) noted differences in control subjects based on catechol-O-methyltransferase (COMT) polymorphisms in the M100 ERF gating patterns to pairs of auditory clicks (94). COMT is an enzyme involved in the degradation of catecholamines, such as dopamine, and polymorphisms of COMT lead to remarkable differences in habituation (response reduced to the onset of the second sound as compared with the first) in the left hemisphere. As the cost of genotyping decreases and the availability of genomic science infrastructure increases, combining genotyping with E/MEG will become more widespread.

40.2. X-Ray Transmission CT

Imaging anatomy with conventional x-rays and film or fluoroscopic screen has several inherent limitations. The projection of a 3-D structure, such as the skeleton, onto a two-dimensional (2-D) film obscures much detail. Films and screens are not sensitive to subtle changes in radiation necessary to resolve fine structure. The large x-ray beams used for conventional radiography produce much scattered radiation, further reducing contrast and resolution. The development of tomographic techniques addressed these limitations, providing an unsurpassed ability to image body structure in most hospitals by the late 1970s. *Tomography* (from the Greek, tomos, meaning section) is the generation of a 2-D image from angular views or projections obtained by detectors placed or rotated around the head or other body part.

Conceptually, x-ray transmission CT uses an x-ray gun that emits a beam of x-rays through the body and an x-ray detector on the opposite side to the gun. The narrow, nearly monoenergetic x-ray beam with intensity I_o passes through the body, becomes attenuated, and gets detected as intensity I. The definition of attenuation coefficient, μ, follows:

$$I/I_o = e^{-\mu x}$$

where x is the thickness of the body through which the x-ray passes. The solution is to take many measurements all the way around the body. Then, the computer can be used to reconstruct the distribution of different "μ"s throughout the body through which the x-ray passes.

$$\text{CT number} = 1{,}000\left(\mu - \mu w\right)/\mu w$$

where μw is the linear attenuation coefficient for water. The CT numbers range from +1,000 for bone to -1,000 for air, with water at 0. In contrast, μ for bone, water, and air are 0.528 cm^{-1}, 0.206 cm^{-1}, and 0.0004 cm^{-1}, respectively. The process by which the image is generated from the raw CT data is termed reconstruction. The typical radiation dose for a CT scan of the head is approximately 3 to 5 rad. The CT data also can be used to determine an important parameter for modeling PET data. Since the various tissues of the head absorb some of the radioactivity, what is termed an "attenuation" scan is critical to modeling of PET data. The typical attenuation scans are acquired with the CT part of PET/CT combination scanners. For PET scanners without CT, rotating gamma emitting rods containing ^{68}Germanium, a positron emitter, accomplish the goal during what is termed a separate "transmission" PET scan that is used to correct the tissue absorptions in the modeling of the injected isotope "emission" scans. The CT attenuation scan and PET transmission scan both accomplish the same goal of providing an "attenuation image", which is used to correct the data from functional emission scans, which are obtained by injecting the subject or patient with a positron emitting isotope, e.g., ^{18}F, ^{15}O, ^{11}C. (http://www.med.harvard.edu/jpnm/chetan/petct/petct.html). However, either the use of CT or the use of the radioactive rod PET scan for attenuation image correction of PET scans requires less radiation exposure than a high-quality CT scan used for diagnostic purposes.

40.3. Magnetic Resonance Imaging

The magnetic properties of fresh and oxygenated blood have been known since the 1930s (95), but the idea of using deoxygenated blood as an endogenous paramagnetic contrast agent had to wait for the post-World War II boom in nuclear magnetic resonance technology (96, 97) and the discovery, two decades later, that the application of imaging gradients in addition to a static magnetic field could provide localization of signal (98, 99). Magnetic resonance imaging (MRI) became clinically applicable in the 1980s (100–104), providing a wide range of contrast mechanisms for visualizing soft tissue and tissue properties such as perfusion.

For most MRI images, the signal comes from hydrogen nuclei (protons) on water molecules, which possess intrinsic magnetic moments and therefore interacts with the strong magnetic field of the MRI scanner. A radio frequency (RF) excitation pulse is used to create a detectable MR signal by perturbing the protons away from magnetic equilibrium, and images are formed using characteristics of the signal that is detected as the protons return to equilibrium. The rate at which the signal

decays ($1/T_2$) and the rate at which the protons return to equilibrium ($1/T_1$) provide information about the local (microscopic) magnetic field environment and thereby tissue type, perfusion or tissue integrity.

Functional MRI—the measurement of perfusion and blood oxygenation changes as an indication of changing states in underlying neural activity—dates to the early 1990s (99, 100). While many studies have found good correlation between fMRI and underlying neural activity, a good understanding of the fMRI signal source and mechanisms of neurohemodynamic coupling is required for accurate interpretation of fMRI data and an understanding of the strengths and limitations of the technique.

40.3.1. BOLD fMRI

By far the dominant form of fMRI is blood oxygenation level-dependent (BOLD) fMRI, the fMRI technique that relies on deoxyhemoglobin as an endogenous contrast agent. Brain tissue, like most body tissue, is diamagnetic, which means that it has a negative magnetic susceptibility and slightly opposes the external magnetic field when a subject is placed in the scanner. As Linus Pauling and Charles Correll deduced in 1936, fully oxygenated hemoglobin has no unpaired electrons and is therefore also diamagnetic, offering no contrast with the surrounding tissue. Deoxygenated hemoglobin, however, is paramagnetic, containing many unpaired electrons that each add minute enhancements to the local magnetic field. This perturbation of the magnetic field results in a decreased signal intensity in MR images, if they are acquired in such a way as to be sensitive to microscopic magnetic field homogeneity (T_2*-weighted images). The resulting contrast between the magnetic field in and around veins and the magnetic field in fully oxygenated tissue is the source of the BOLD signal.

40.3.1.1. History

Early fMRI experiments set the tone for the next 15 years of research on BOLD mechanisms. In the experiment reported by Ogawa et al. [1993; (105)] visual stimulus was provided by LEDs mounted in a pair of goggles worn by the subject. The MR signal was measured in a single imaging plane through the occipital cortex, where primary visual areas are located, while the stimulus was alternated between flashing LEDs and rest. During stimulation blocks, intensity increases were measured in small areas in posterior occipital cortex. This experiment had two key results: the signal changes were localized to small regions of the brain, and the signal changes were positive. Measurement of isolated regions of BOLD response indicated that hemodynamic changes could be specific to active regions of cortex. The fact that the signal changes were positive indicated that a net decrease, rather than increase, of local deoxyhemoglobin was the result of visual stimulation.

The positive BOLD signal was not surprising in view of positron emission tomography (PET) studies that had shown an apparent overcompensation of blood flow in response to brain activation (106). At rest, the blood in arteries is fully oxygenated and venous blood is approximately 60% oxygenated. During stimulation the cerebral metabolic rate of oxygen consumption ($CMRO_2$) only increases by approximately 5% during focal neural stimulation, while local blood flow can increase by as much as 50%. This large blood flow increase in response to stimulation, which more than compensates for increased oxygen consumption, results in a venous oxygenation of approximately 80% during stimulation. Thus, the net BOLD response to stimulation is typically an increase in signal intensity due to a reduction in venous deoxyhemoglobin concentration.

40.3.1.2. The Hemodynamic Response

The term hemodynamic response is used to describe the changes in blood flow, blood oxygenation and blood volume that combine to create the measured fMRI contrast. While variations will be discussed later, the typical BOLD hemodynamic response is described here. After a brief neural stimulus, blood flow begins to increase after a delay of 1–2 seconds. The increase in flow results in a decrease in venous deoxyhemoglobin concentration, and therefore an increase in image intensity in a T_2*-weighted image. The latency of the BOLD response varies from individual to individual, and from one region of the brain to the next (107, 108). The latency is also longer in large veins than it is in small veins (109), but an average response will peak 5–6 seconds after stimulus onset. If the stimulus is sustained, as in an experiment using a block design in which stimuli are presented continually for 10 or 20 seconds, the BOLD response will remain elevated (but not necessarily constant) during the entire stimulus period. The offset of the hemodynamic response is more rapid than the onset, so the BOLD signal begins to decrease almost immediately after the end of a sustained stimulus. The signal does not, however, simply return to baseline. There is a post-stimulus undershoot that lasts approximately 10 seconds (again, this is dependent on the individual subject and details of the stimulus) before the hemodynamic response resolves itself fully and returns to baseline. BOLD signal changes are calculated on a relative scale, as percent modulation of resting-state or baseline activity.

One model for the different factors that contribute to the hemodynamic response is the Balloon Model (110). This model separately considers the following contributions to the hemodynamic response:

1) *Oxygen consumption*. The metabolic demand of pre- and post-synaptic activity and generation of action potentials in neural communication results in increased demand for oxygen. Of these different aspects of neural coding, post-synaptic activity and integration of dendritic information are predicted to be the most metabolically demanding, (111) and, therefore, most tightly coupled to the hemodynamic response. While increases in oxygen consumption are modest (5% increase in $CMRO_2$, as mentioned above), they nonetheless result in a decreased signal intensity in T_2*-weighted images.
2) *Blood flow*. Increased oxygen demand must be met by increased blood flow. Mechanisms of neurohemodynamic coupling are not fully understood, but some combination of NO (112), extracellular K+ (113) and glutamate (114), and direct innervation of smooth muscle cells results in an increase in blood flow (and therefore local supply of glucose and oxygen) when neural activity increases (115).
3) *Blood volume*. The walls of veins are not rigid, and the increase in blood flow results in an increase in blood volume. At rest, the venous compartment of the vasculature occupies approximately 2% of the cortex volume. After stimulation, this can increase to almost 3% (101). A combination of delayed venous compliance (116) and reduced deoxyhemoglobin concentration generates the post-stimulus undershoot in the BOLD signal.

40.3.1.3. Spatial Resolution

Researchers investigating BOLD contrast mechanisms use stimuli more sophisticated than those used in the first experiments, but the focus of the research remains the same: what is the spatial specificity of the BOLD response, and how do the amplitude and timing of the hemodynamic response relate to underlying neural activity? Early concerns that blood flow was regulated on only a coarse scale were put to rest by the success of optical imaging of the fine structure of ocular dominance and orientation columns (117). Subsequent imaging of columns using fMRI techniques such as cerebral blood flow (CBF) and differential BOLD techniques (118, 119), as well as the observation of control points strategically positioned on small arteries and capillaries (120) ensured blood flow regulation was finely tuned. BOLD contrast, however, originates from changes in deoxyhemoglobin concentrations in veins. As imaging technologies improve, and we are capable of acquiring higher resolution images in shorter times, it is important to understand if the underlying BOLD signal has the same spatial resolution as our image.

The majority of BOLD fMRI studies employ gradient echo BOLD. The term "gradient echo" refers to the pulse sequence, which determines how the image data are collected. A gradient echo (GE) pulse sequence will produce an image that is sensitive to T_2*, the time constant that describes how the decay of excited magnetization is affected by local (microscopic) field perturbations. The strongest GE BOLD contrast comes from large veins on the pial surface, which have the highest deoxyhemoglobin concentrations and therefore the strongest BOLD contrast. Large veins collect blood from the largest cortical territories and both blur and displace BOLD contrast (121–124). For many studies, this is acceptable: even though large veins pool signal from a relatively large region of cortex (~5 mm in diameter), higher resolution is not required. But for studies seeking to study neural activity on the scale of cortical columns (~1 mm), the BOLD contrast from large veins is undesirable.

As an alternative to gradient echo pulse sequences, spin echo (SE) pulse sequences employ an additional refocusing pulse between excitation and image acquisition. If water molecules were perfectly stationary during the imaging time, SE pulse sequences would measure no BOLD contrast because the effects of field inhomogeneities (T_2* effects) would be completely refocused or erased. However, diffusion results in motion of water molecules during the imaging time, and the refocusing pulse fails to erase BOLD contrast inside large veins and in the tissue surrounding veins with a small diameter (capillaries and intracortical venules). At low and moderate magnetic fields, the fact that signal is refocused in venous blood (intravascular effects) means that SE-based BOLD fMRI offers no advantage for spatial resolution. But at very high magnetic fields, the short T_2 of blood [compared to the tissue; (125)] erases the intravascular contribution of large veins. Thus SE BOLD at 7 T is primarily sensitive to capillaries and small intracortical veins (126). The concomitant reduction in contrast-to-noise ratio (127) requires an increase in the number of trials required to reach significance in a given experiment, relative to the same experiment measured with GE BOLD, but the measured voxel responses have greatly improved spatial specificity. The potential for high spatial resolution with ultra high-field fMRI is one reason that a growing number of research sites are installing commercially produced 7 Tesla scanners.

40.3.1.4. Challenges for Functional MRI

While BOLD-based fMRI techniques have great potential for revealing neural mechanisms of behavior and perception, the techniques also have substantial limitations. One notable limitation is the difficulty of acquiring distortion-free images with good signal-to-noise ratio (SNR) in inferior regions of the brain. Acquiring an accurate MRI image, particularly with the long

acquisition times used in functional MRI experiments, requires a uniform magnetic field. The magnetic field in the scanner is uniform before the subject is moved into the bore of the scanner, but the magnetic susceptibility of the subject's tissue perturbs the field. Generally, the perturbations are smooth and a process called shimming compensates for the distortions. But around bone and regions with abrupt transitions between air and tissue (most notably for brain imaging, regions near the auditory canals and frontal sinuses), the field perturbations are abrupt and only partially compensated by shimming.

A poorly shimmed sample will result in at least two types of image artifacts: distortion and drop-out of signal due to through slice dephasing. Distortion arises because signal localization in an MRI system is accomplished with applied magnetic field gradients that establish a relationship between position and local field strength in the sample. When local field strength is perturbed by a source that is not accounted for in the image reconstruction process, the result is an error in localization. The severity of the distortion depends on the details of the image acquisition, but the types of images most commonly used for fMRI (both BOLD-based and perfusion) are the most vulnerable to distortion. With knowledge of the exact field perturbations at the time of acquisition, which can be measured with a short field-mapping pulse sequence, it is possible to correct for distortions before analyzing functional data (128). Adding such a post-processing step can greatly improve the accuracy of signal localization in fMRI studies.

In addition to distortion due to frequency offset errors, fMRI images suffer from signal loss due to through-slice gradients in the field. The signal intensity in any volume element (voxel) is determined by the vector sum of all of the protons in the voxel, each of which processes at a rate determined by the local field strength. When a spurious magnetic field gradient exists in the voxel, the signal is rapidly erased by intra-voxel dephasing of the spins. While post-processing may be able to correct for distortion in functional images, there is nothing to be done to regain the signal once it has been lost. Research on this aspect of artifact compensation therefore focuses on compensating for and avoiding susceptibility-induced gradients at the time of acquisition (129, 130). While spin echo (SE) EPI techniques have lower contrast-to-noise ratio and little advantage for spatial resolution at moderate fields, as discussed above, SE EPI pulse sequences do compensate for the severe through-slice dephasing in orbitofrontal cortex and can detect functional activation that would be lost in gradient echo (GE) EPI.

40.3.2. Perfusion fMRI

Perfusion fMRI experiments measure cerebral blood flow (CBF) changes directly, through a technique known as arterial spin labeling (ASL), without reliance on deoxyhemoglobin as a contrast agent. Many variants on the technique exist, with each new pulse sequence seeking to improve the quantitative aspects or reliability of the technique. Here, we will discuss only the general concept of ASL pulse sequences, referring the interested reader to published literature on individual pulse sequences and their advantages or limitations (131–133).

40.3.2.1. Technique

Where BOLD fMRI relies on T_2* contrast, perfusion uses T_1 properties to detect blood flow changes. The relaxation processes described by T_1 and T_2* occur on very different time scales. After an RF pulse excites spins, the decay of detectable transverse magnetization occurs with a characteristic time constant (T_2*) in the range of 20–100 milliseconds. The return to equilibrium (full recovery of longitudinal magnetization, which is the net magnetization of the sample in the direction of the main magnetic field), occurs with a characteristic time constant (T_1) of 1000–2000 milliseconds. It is this longer timescale that is useful for ASL pulse sequences. In a pulsed ASL sequence, the magnetization of blood flowing into a volume of interest is inverted with a preparation inversion pulse, and then a delay is introduced into the pulse sequence to allow this inverted blood to enter the volume of interest. Arterial transit times over relevant distances (several centimeters) are typically on the order of 700 milliseconds. The longitudinal magnetization in the tagged, or labeled, blood has not recovered to equilibrium values after this delay, so the net magnetization in the volume of interest is the vector sum of the stationary blood (equilibrium magnetization) and the incoming blood (inverted magnetization). The effect of the tagged magnetization is thus to decrease the net magnetization of the volume of interest; the greater the perfusion of the tissue, the greater the reduction of the MR signal from the region of interest. Perfusion is therefore related to the difference in image intensity between a labeled and an unlabeled acquisition. When the labeled and unlabeled images are acquired with a T_2*-weighted EPI pulse sequence, BOLD data are acquired in the course of acquiring the perfusion data.

The perfusion response to neural stimulation is large—often a 50% increase in measured local CBF. The noise in the measurement is, unfortunately, also large, with the result that the contrast-to-noise ratio of perfusion techniques is similar to that of BOLD techniques, in spite of the large signal modulation inherent to the technique.

40.3.2.2. Advantages and Limitations

The great advantage of perfusion fMRI is that it circumvents the venous blurring that is central to concerns about the resolution or localization capabilities of BOLD fMRI. The great disadvantage of ASL sequences is that this improvement in spatial specificity comes at the cost of temporal resolution. The required delay to allow for arterial transit time places a minimum on how quickly data can be acquired; the need for both labeled and unlabeled images to calculate perfusion from subtraction then doubles the minimum time required to acquire a volume of data. Many block design experiments, however, can tolerate this relatively low temporal resolution and improve spatial specificity, such as during visual stimulation.

40.3.3. Anatomical Magnetic Resonance Imaging

Whether form follows function, or function follows form, it is increasingly clear that structural measurements and measurements of connectivity between different brain regions hold some of the keys for unlocking questions about brain function in health and disease. In some cases researchers may not know what behavioral or cognitive tasks can be used to elicit functional differences between two populations, or the differences in question may not be easily adapted to an hour-long experiment in a scanner. Yet in these cases, MRI still offers the ability to study neurological differences via structural and anatomical imaging.

40.3.3.1. Structural Imaging

While the achievable resolution in functional MRI experiments is limited by the desire to image the entire brain volume in a few seconds, the limitation to resolution in structural imaging experiments is more commonly the signal-to-noise ratio (SNR), which to a first approximation is directly proportional to the volume of the voxel. Doubling the resolution (from 1 mm isotropic to 0.5 mm isotropic voxels, for example) represents a loss of a factor of 8 in the SNR. SNR can be regained by averaging together multiple image acquisitions, but time constraints rapidly make this impractical (regaining a factor of 8 in SNR would require averaging 64 independent acquisitions).

Two very attractive approaches to increasing the SNR in an MRI system are to decrease the image acquisition time with parallel imaging (134–136) and to increase the field strength (137, 138). While parallel imaging offers temporal and spatial resolution gains for fMRI, the gains are often greater for anatomical acquisitions. In general, the image SNR increases linearly with the field strength, so a 3 T clinical scanner should offer approximately twice the SNR available at 1.5 T. SNR is also dependent on many aspects of the hardware, most notably the type and quality of radio frequency coil used to receive the signal, but also the bandwidth of the receiver and the speed of the imaging gradients, so there are no hard and fast rules about SNR. The trends, however, are toward higher field strengths, faster gradients, and arrays of surface coils used to receive (or transmit) the signal in parallel each of these technological advances increases the SNR and/or decreases the acquisition time, thereby enabling better images at higher resolution.

An example representing perhaps the extremes of the information available in structural imaging is cortical degeneration in Alzheimer's disease. On a macroscopic scale, MRI scans show widening of sulci and loss of gray matter (139). On a microscopic scale, MRI scans can detect the formation of Alzheimer's plaques in mouse models of the disease (140), offering potential for early detection and an improved understanding of the molecular mechanisms. Other examples of clinically relevant structural findings are increased gyrification in Williams's syndrome (141), decreased hippocampal volume in depression (142), and progressive loss of gray matter in schizophrenia (143).

40.3.3.2. Diffusion Tensor Imaging

While tissue relaxation times are the primary contrast mechanism used in functional (T_2*) and structural (T_2 and T_1) MRI, it is also possible to acquire images in which the contrast is generated by the motion of water molecules during the image acquisition. Diffusion was discussed earlier as the source of contrast in spin echo BOLD fMRI acquisitions, but it is also useful as an indicator of the primary orientation of white matter tracts in the brain. The acquisition of diffusion-weighted images requires strong imaging gradients, but advances in technology have enabled this powerful tool for investigation of white matter integrity and connectivity between multiple brain regions.

A diffusion-weighted sequence applies a pair of strong diffusion gradients after tissue excitation and before image acquisition, usually on either side of a 180° refocusing pulse (144). Stationary spins (protons on water molecules) experience balanced effects from the bipolar gradients, and the signals from these spins are not attenuated. However, when a molecule diffuses a significant distance between the applications of the first and second gradient, the effects of the gradients are no

longer balanced and the signal is attenuated (by intra-voxel dephasing). Acquiring a series of images with gradients applied along different axes provides the data for mapping the preferred direction of diffusion in each voxel.

Once diffusion weighted images are acquired, data analysis can take many directions. One parameter that is clinically useful is *fractional anisotropy*. Where diffusion is isotropic, signal intensity does not depend on the axis along which diffusion gradients are applied. This behavior is expected in compartments with unconstrained diffusion such as cerebral spinal fluid. In white matter, however, the myelination of the axons and the bundling of axons into fascicles constrain the diffusion of water molecules, so greater diffusion will be measured in a direction parallel to the dominant orientation of axons. The anisotropy of diffusion is therefore an indication of local organization of white matter; decreased fractional anisotropy is correlated with reading impairment in dyslexia (145) and axon degeneration in multiple sclerosis (146), to name a few examples.

Diffusion tensors can also be calculated from the fractional anisotropy data and used to characterize the major and minor axes describing diffusion in each voxel. An intriguing application of diffusion tensor imaging (DTI) is tract tracing–seeding a voxel in one region of the brain, and following the major axes of the diffusion tensors in this and subsequent voxels to discover what other regions of the brain might have strong anatomical connections with the seed region. An active area of research considers the right computational approach to take when two bundles of axons cross each other, resulting in a voxel that has a low fractional anisotropy in spite of the fact that it contains strongly oriented white matter subsets. Tractography has nonetheless been used to trace anatomical connectivity in, for example, healthy and motor-impaired individuals (147).

40.3.3.3. Functional Connectivity

An emerging branch of fMRI considers resting state or intrinsic correlations between blood flow changes in multiple brain regions as an indication of functional, as opposed to anatomical, connectivity between these regions. The logic underlying resting-state measures of functional connectivity is the following: if neurons in one region make synaptic contact with neurons in a second region, then action potentials (and therefore hemodynamic fluctuations) generated during a resting state in one region will be correlated with resting state hemodynamic signal in the second region (148). Intra-region correlations in the BOLD fMRI signal during a task have also been used to probe the strength of connectivity between multiple brain regions, providing yet another tool for studying coordination of distributed networks involved in complex cognitive tasks (149).

40.3.4. Spectroscopy

While the dominant forms of spectroscopy are not, strictly speaking, imaging, no discussion of the applications of MRI to studying the brain would be complete without at least a brief mention of spectroscopy. The resonant frequency of a particular magnetically active nucleus (^{1}H, ^{13}C, ^{17}O and ^{31}P being notable in biological applications) is determined by its molecular environment, and in vivo NMR spectroscopy has the ability to detect the relative concentrations of hundreds of different molecules. If the SNR and resolution of imaging applications benefit from increased field strength, spectroscopy benefits all the more. Chemical shift imaging can detect the distribution of molecular markers across the brain, and localized (single-voxel) spectroscopy has the ability to detect small shifts in molecular concentrations as a result of functional activation (150) or disease (151, 152).

40.3.5. Summary of MRI Techniques

The MRI community has just begun to explore relevant contrast mechanisms in the brain. BOLD fMRI dominates the field because this technique offers rapid, non-invasive measurement of changes in blood flow and oxygenation that are related to cognitive state or behavioral task. There is, however, a wealth of other MRI contrast mechanisms available for studying the neural substrates of behavior, including (but not limited to) perfusion, diffusion, spectroscopy and structural MRI. Magnetic resonance imaging is ensured a place in the neuroscientist's and clinician's toolbox as increasing field strength and faster parallel imaging methods enable higher resolution and better contrast. Functional activation and connectivity measures of fMRI data have elucidated cognitive and affective mechanisms of neuropsychiatric disease. For example Palaniyappan et al. (2013) (153) have used Granger causal modeling of cognitive tasks to reveal dysfunctional processing of information in patients with schizophrenia (see Fig. 40.3).

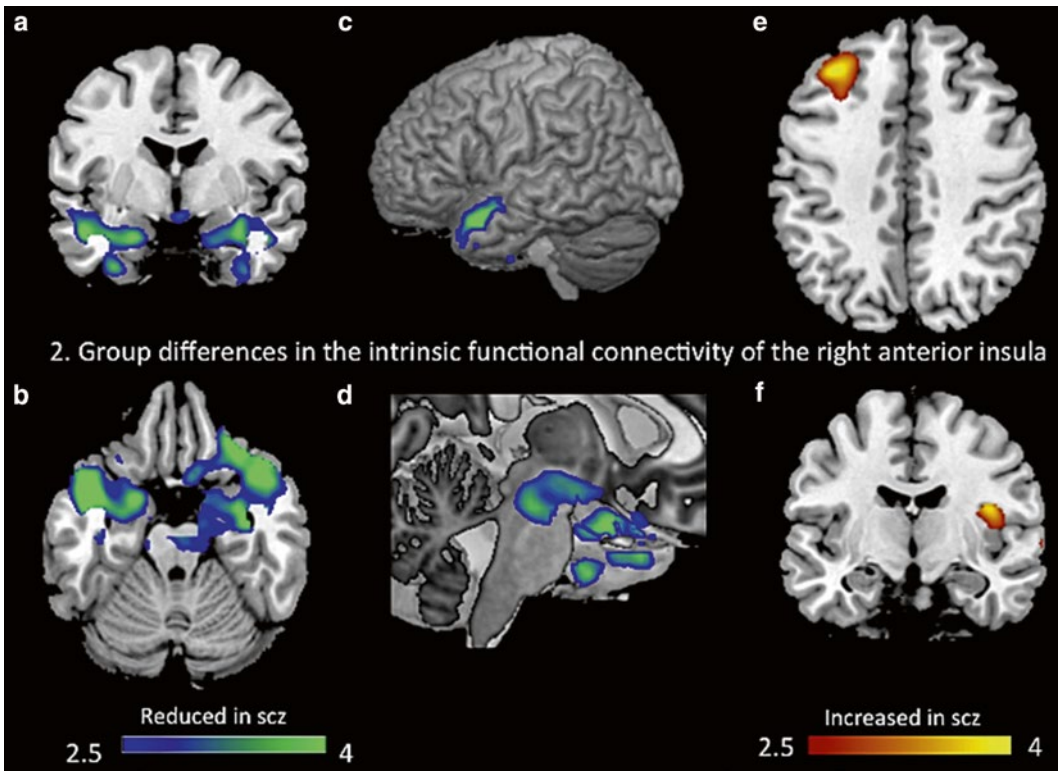

FIGURE 40.3. The influence of rest of the brain on rDLPFC (y to x). The figures show the results of the one-sample t test of Granger Causality Analysis maps on all subjects (schizophrenia patients and controls). Illustrations drawn on a single subject structural image showing axial slices using xj view at $p < 0.001$ uncorrected, but with an extent of activity criterion of $k = 30$. Color bar shows a scale of T values. Warm colors suggest excitatory influence, while cold colors suggest inhibitory influence. Reprinted from Palaniyappan et al. (153) copyright (2013) with kind permission from the author under Creative Commons Attribution-NonCommercial-No Derivative Works License.

40.3.6. Molecular Imaging

40.3.6.1. Introduction to Molecular Imaging

The use of radioisotopes in medicine has enabled the detection of disease processes with unparalleled sensitivity. In the near future, the non-invasive measurement of molecules and gene expression, as well as the ability to sequence the individual patient's genome, will usher a new era in medicine. Both instrumentation and novel techniques are advancing rapidly. This progress has come in part from the development of computed tomography, so greatly dependent upon computer science and faster, more powerful computers. Today, such technology is an essential component of the armamentarium for the clinician's use in diagnosis, prognosis, and treatment. The gamma camera (also called Anger or scintillation camera) was among the earliest technology to visualize molecules non-invasively in humans. It remains in widespread use even today. Isotopes emitting gamma radiation, because of the higher energy, permit radiation from deep organs to exit the body for external detection. For brain imaging, single photon emission tomography (SPECT) and positron emission tomography (PET) make up the most frequently used nuclear medicine technologies. Application to the clinical setting requires algorithms for image reconstruction and high speed computers for efficient production of images. With the widespread availability of both SPECT and PET, these imaging technologies offer psychiatry what the microscope offered pathology in the last century. One of the concerns associated with the use of these techniques is widespread misunderstanding and lack of education about radiation exposure and its effects upon the body.

40.3.6.2. Radiation Exposure

Although highly sensitive with capability for measuring sub-nanomolar quantities of molecules, a disadvantage of these methods arises from concerns about exposure to radiation. Unfortunately, the general population often lacks education about

TABLE 40.1. Units of measurement used frequently in nuclear medicine.

Measurement	Traditional units	Systemional unitsent used f
Radioactivity	Curie (Ci) $3.7(10)^{10}$ dps*	Bequerel (Bq) 1 dps
Exposure	Roentgen	$2.58(10)^{-4}$ coulombs/kg
Absorbed dose	Rad	0.01 grey (Gy)
Absorbed dose equivalent Effective dose equivalent	Rem	0.01 Sievert (Sv)

*dps, disintegrations per second.

radiation exposure, and the very word "nuclear" becomes cause for alarm. Not surprisingly, the word "nuclear" has been dropped from technologies such as nuclear magnetic resonance imaging. Survivors of atomic bombs do develop leukemias years after exposure, but what is known about radiation exposure in the medical setting?

Radiation exposure has both stochastic (i.e., random, probabilistic) as well as non-stochastic (i.e., predictable, dose-related) components. Stochastic processes are characterized by a relationship between dose and the probability of an effect; lack of relationship between dose and the severity of the effect for an individual; and no minimum threshold. The latter implies that there is no level of radiation below which the effect will not occur.

Low level exposure is thought to cause stochastic effects. Stochastic effects of radiation include carcinogenesis, teratogenesis, and mutagenesis. Non-stochastic effects include "radiation sickness," or more properly termed acute radiation syndrome, which occurs when rapidly dividing cells or stem cells are exposed to high levels of radiation over a brief period of time. The systems typically involved are the skin, gastrointestinal tract and the bone marrow. The effects to the gastrointestinal tract include diarrhea, electrolyte imbalance, hemorrhage, and dehydration. The effects to the bone marrow result in leucopenia, thrombocytopenia, and anemia, etc. With very high radiation exposures, a cerebrovascular syndrome occurs that is life threatening usually from vascular damage to the brain and neuronal death.

Radiation exposure in medicine typically does *not* involve non-stochastic processes. Several units of measurement under two systems are used to quantify radiation exposure (Traditional, T or Système International, SI; Table 40.1). The amount of radioactivity is measured in disintegrations per second (dps). A curie (Ci; T) is $3.7(10)^{10}$ dps. One disintegration per second is a becquerel (Bq; SI). The roentgen measures *exposure* in the traditional system and equals $2.58(10)^{-4}$ coulombs/kg (SI). The amount of energy absorbed in a medium from radiation exposure (i.e., joules/kg) is called the *absorbed dose* in units of rad (*r*adiation *a*bsorbed *d*ose; T) that equals 0.01 Grey (Gy; SI). Because a given absorbed dose may have differing biological effects depending on several factors (e.g., sensitivity of tissue to radiation; damage to cells caused by different types of radiation; the effects to the health of the individual as a whole; impact upon future generations), the concept of the *absorbed dose equivalent* was developed. The absorbed dose equivalent has units of rem (T) or 0.01 Sievert (Sv; SI). Different types of radiation cause different degrees of biological damage. For example, alpha particles cause far more damage than X-rays. Therefore, the *quality factor* was developed to adjust for the effects of different types of radiation.

Dose equivalent (H in units of Sv) = Absorbed dose (D in units of Gy) x Quality factor (Q in units of Sv/Gy). The Q for most of the radiation (X rays; γ rays; and β particles) discussed here is 1 Sv/Gy. It is possible to better quantitate the overall detriment to the subject. For example, X-rays (Q = 1 Sv/Gy) applied to the bladder have relatively little detriment to the patient. The same X-ray absorbed dose administered to the lens may cause cataracts (as does solar radiation), but not death. The same absorbed dose to the bone marrow has more detriment because of the susceptibility of the hematopoietic system and its vital importance to survival. To get a handle on the problem, the concept of *effective dose equivalent* was developed. Data from epidemiological studies about detriment of radiation to different organs produced a tabulation of weighting factors for different tissues. Multiplication of the tissue-specific weighting factor by the dose equivalent to that organ yields the effective dose equivalent.

The organization charged with developing safety recommendations and promoting consensus is the International Commission on Radiological Protection (ICRP). Of note, the risks from radiation exposure of most medical imaging procedures are so small, that there are no firm limits concerning radiation exposure *when medically necessary and appropriate.* This does not apply to the use of radiation therapy in medical oncology where the doses have important non-stochastic effects and where the goal is to destroy cancer cells. Also, this is not the case when using radioisotopes for research, where the primary interest is not the diagnosis or treatment of a disease. The Food and Drug Administration (FDA) monitors use of radioisotopes in research on humans. By law, the effective dose from administration of radioisotopes to research subjects must stay within the guidelines in Table 40.2. Further, the FDA requires that the institution where the work is done have a Radioactive Drug Research Committee (RDRC), which must approve research protocols using radiation, monitor dosing and number of subjects studied, and provide annual reports to the FDA. If a protocol will use more than 30 subjects, the RDRC will require additional documentation of the rationale and need for subjects as well as additional paperwork and reporting requirements.

TABLE 40.2. Annual, adult radiation dose limits (rems) for radioactive drugs and procedures for research studies (21CFR361.1, U.S. code of federal regulations).

	Dose (rems)
Whole body, active blood forming organs, lens of the eye, gonads	
Single dose	3
Annual and total dose commitment	5
Other organs	
Single Dose	5
Annual and total dose commitment	15

TABLE 40.3. Equivalent risks to one in a million chance of death.

One in a million risk of death	
Risk	Cause of death
10 millirems radiation	Cancer
10 miles bicycle riding	Accident
300 miles car travel	Accident
Smoking 1.4 cigarettes once	Cancer
Drinking 30 cans of diet soda	Cancer
Working 10 days in a factory	Accident
16 days of cabin crew flying at 35,000 ft	Cancer

Because a large amount of radiation can cause cancer, it is assumed that smaller exposures have a smaller chance of this bad effect. In reality, this assumption is probably an overestimation because the body's DNA repair mechanisms can handle low level exposure. The average person gets 22.5 rems of radiation exposure over an assumed lifespan of 75 years. Medical X-rays can expose the patient to as little as 10 millirems or up to 10 rems or more. To put the risks of radiation exposure into a context that lay persons can better appreciate, Table 40.3 shows equivalent risks with respect to common daily activities. For example, exposure to background radiation from natural sources is about 300 millirems per year. Cabin crews of airlines get an additional 227 millirems per year from cosmic radiation by flying at 35,000 feet above sea level (154). The risk for many nuclear medicine studies is no greater than the additional exposure a traveler receives by flying roundtrip between Los Angeles and New York. Thus, while the potential consequence of radiation exposure is grave, the chance of getting such an outcome is rare. Therefore, it is prudent to minimize radiation exposure, but irrational fears would necessitate never getting into an airplane.

40.3.6.3. Three Dimensional (3-D) Imaging: Principles

Clinicians are familiar with standard X-ray representations of a patient's body. The image is simply a projection of a 3-D structure unto a 2-D plane such as film or a pixel array in an electronic camera. A revolution in imaging arose with Sir Godfrey Hounsfield's development of tomographic principles which led him along with A. M. Cormack to win the Nobel Prize in Medicine and Physiology in 1979. The development of modern, high speed computers brought computerized tomography into a clinical reality.

The concepts developed by Sir Hounsfield received broad application in nuclear medicine. They served as the foundation for both single photon emission computed tomography (SPECT) and positron emission tomography (PET). *Tomography* (from the Greek, tomos, meaning section) is the generation of a 2-D image from angular views or projections obtained by detectors placed or rotated around the head or other body part. Emission computed tomography is the reconstruction of an image from projections of the distribution of radioactivity. The emissions are gamma rays so they can pass through the body to reach external detectors.

The principles of tomography can be presented simply without the underlying mathematical formulas used by the computer which is beyond the scope here. Suppose someone has severe myopia, and their eye glasses are lost. Given the need to read a distant sign, how might the problem get corrected? The easiest solution is to make a pinhole in a piece of paper and to look through the hole. The sign will be clearly visible because only the direct, parallel light rays from the sign will fall upon the center of the eye lens where no distortion will occur, while blocking rays from entering other parts of the lens at different angles otherwise causing visual distortion.

Tomography exploits an analogous process. The 2-D case provides an easy heuristic; the 3-D example can simply consist of a stack of 2-D images. Figure 40.4 shows it is possible to project the distribution of radioactivity, f(x,y), in a plane using rays that are parallel and perpendicular (termed lines of response at angle θ) onto line **l.** The result is a function, $p(\theta, r)$, p for profile, whose ordinate is the integrated radioactivity (i.e., counts per time interval for the cylinder of tissue) projected along

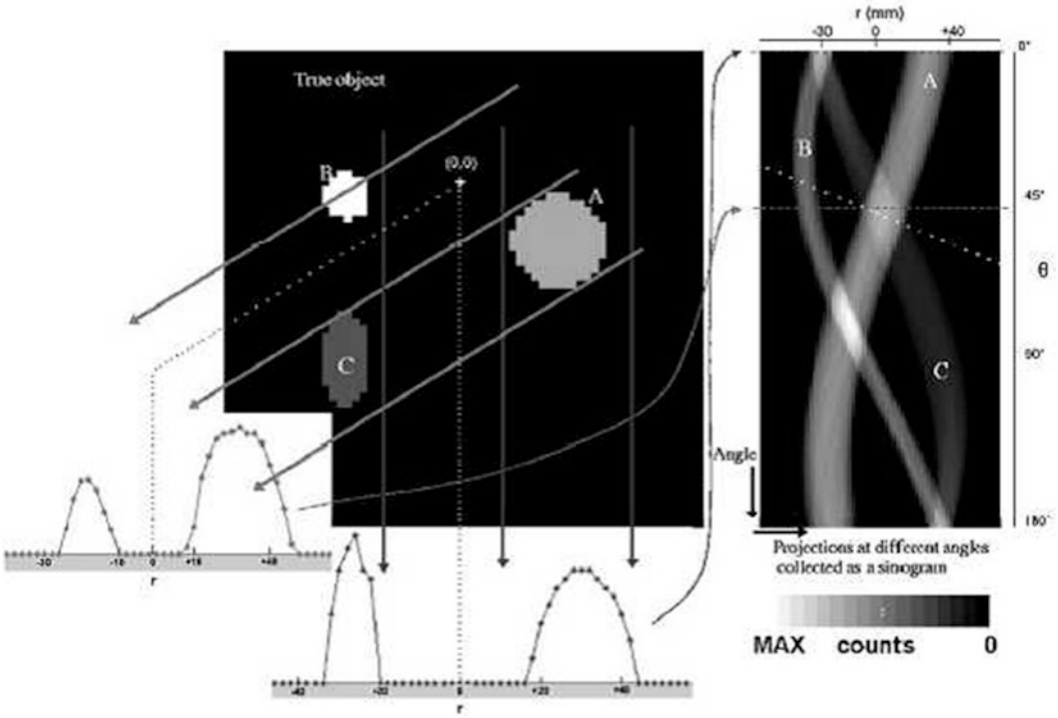

FIGURE 40.4. Emission computed tomography of three radioactive objects (labeled A, B, C) described by the distribution of radioactivity, f(x,y), in a plane. A 3-D radioactive object can be considered as a stack of such planes. Brightness in the picture denotes amount of radioactivity: the greater the radioactivity, the brighter the object. This assignment is coded through a grey scale (see bottom of right of figure) that in this case goes from black (no radioactivity) to white (maximum, MAX, of radioactivity). So, object B is the most radioactive and is brightest, while object C is the least radioactive and is darkest. The origin of the activity distribution, f(x,y), is labeled (0,0), typically the center of the field of view of the camera. In this figure, the projection angle θ is measured for illustrative purposes from the negative y axis. The projection p(θ, r) to θ=0° is downward and is shown at the bottom of the figure. The ordinate of the projection profile, p (0,r), is the number of radioactive counts measured at θ=0° as a function of r, the distance from the origin. Note that r=0 corresponds to the projection of the radioactivity at the origin at a particular θ. It happens that at θ=0° objects B and C overlap while θ=45° objects A and C overlap. The ordinate of p(θ, r) is the radiation counts typically accumulated during the time interval of the scan (which can thus be converted to counts per second). The amount of radioactivity reflects radiation projected from a narrow column of tissue at position (θ, r). The size of the narrow column is related to the collimator in SPECT or to the crystal distribution for coincidence detection in PET. A sinogram (right) is a 2-D representation of all the projection profiles: brightness (per grey scale) reflects increasing amount of counts; the horizontal axis is r; the vertical axis is θ. Note that this representation is termed a sinogram because of the sinusoidal curves resulting from the projection profiles. One projection profile (here showing only θ=0° and 45°) is one horizontal line of the sinogram (curved arrows link the projection profile to the corresponding straight line in the sinogram). Note that each object in the sinogram becomes represented as a sine wave whose width corresponds to the width of the object and whose brightness corresponds to the level of radioactivity in the object. Note that when a projection results in the superimposition of two objects (e.g., the projection at 0° degrees superimposes objects B and C, the corresponding sinogram shows two sinusoids crossing, and the crossing becomes brighter (summation with more total radiation). Suppose a group (also called a block) of detectors gets damaged and does not detect any radiation. A corresponding dark diagonal streak will appear in the sinograms. Since only the projections involving these detectors will be affected, the streak will span only a limited subset of projection angles in the sinogram. For example if the broken detectors are at -45°, the projections at -180° will be unaffected. However, the absence of counts from the broken detectors will span the full range of r. The broken detectors will appear at different r's in each and every projection. For illustration of such detector failure at θ=-45°, a white dotted line identifies the position of the dark streak in the sinogram. The sinogram is a valuable representation of the integrity of the data acquisition for emission tomography and can quickly identify hardware problems. Sinograms are critical for checking for uniform sensitivity in emission tomography in the field of view of the scanner.

the rays perpendicular to l. In other words $p(\theta, r)$, represents the counts taken from projecting the object's emissions along lines of response at position r and at angle θ. How this differs fundamentally from SPECT and PET will be discussed in the respective sections below. The origin of the l can be considered arbitrarily the center of the activity distribution, which is typically placed in the center of the scanner's field of view. The function $p(\theta, r)$ is called a projection profile. Figure 40.4 shows the data from two projections from three objects. To cover the entire distribution, additional projections can be collected (e.g., θ=0 to 360 degrees). Note that the projection data at 0 and 180 degrees are the same, but obtained in reverse

direction. An efficient way to represent all these data plots θ on the ordinate and r on abscissa. The counts collected for each projection $p(\theta, r)$ are represented by the intensity of the line at the point; black denotes no counts, and white denotes high counts. This plot is termed a *sinogram* because of the sinusoidal variation of positions of projections through the radioactivity distribution as a function of rotation (Fig. 40.4).

One sinogram contains all the data for one image. The projection-slice theorem states that the actual radioactivity distribution can be calculated perfectly given an infinite number of projections and infinite number of angles. Of course, the final object is less accurately determined given that in reality only a limited number of projections and angles are obtained. The sinogram allows easy detection of problems with the scanner. The scanner is checked daily both with no activity in the field of view ("blank" scan) or with a predetermined amount of radioactivity ("normalization" scan) that permits adjustment of the detector sensitivities within and across planes.

The process of converting the sinogram data to an image is termed *reconstruction*. There are many algorithms to achieve reconstruction. Historically, *filtered back-projection* was the most common technique when computers were slower, and imaging conditions were less than ideal. This algorithm uses $p(\theta, r)$ and projects the data back into the field of view of the scanner using lines of response (parallel, perpendicular rays to l) as used originally to obtain the projection profile. When multiple profiles are back-projected, the projections interact constructively and the original distribution of radioactivity begins to take form (Fig. 40.4). A problem with filtered back-projection is smearing of activity that appears like spokes on a wheel. No matter how many projections, this smearing will persist. A filter applied to the data can decrease this blurring.

An alternative technique that is becoming more widely used with faster computers is *iterative reconstruction.* There are several advantages to iterative reconstruction as compared to filtered back-projection: decreased sensitivity to noise; more optimal image reconstruction when projections are sparse or missing at certain orientations; better performance when projection sampling is non-uniform; and decreased susceptibility to metal artifacts. The method begins with an assumed image perhaps as crude as an ellipse for a transverse section through the head. Given this image, the projection profiles are computed. The method then compares the original to the observed projection data and updates the image based upon the differences. As this difference decreases, the algorithm converges to a final reconstructed image.

Perhaps the most common approach to iterative reconstruction in modern scanners is OS-EM (ordered subsets-expectation maximization). The major advantages of this approach are: 1) faster reconstruction; 2) more accurate modeling of the emission and detection physics; 3) modeling of the statistical properties of noise (e.g., Poisson for radioactive decay); and 4) use of prior data describing the anatomy of the brain area. This method exploits the iterative reconstruction based upon an ordered subset of projections spaced in approximately equal angles (e.g., 4 subsets each at 90 degrees apart). Each reconstruction uses a different set of projections. In this way, almost as accurate a reconstruction can be computed as if all projections were used thus reducing the computation time. Expectation maximization uses two steps. The expectation step predicts the observed projections based upon the current estimate of the distribution of activity. The maximization step uses the difference between the actual and expected activity distributions. This difference is used to adjust statistically the updated activity distribution to maximize the likelihood of the solution.

40.3.6.4. Scintillation, Gamma, or Anger Camera

Hal O. Anger (1920–2005) developed the first gamma scintillation camera in the 1950s. These cameras have several components: collimator, scintillator, light guide, and photomultiplier tubes. As discussed above, a collimator, akin to a pin hole in paper to correct for lens distortion, enables the acquisition of a projection. A large crystal (e.g., 30 cm diameter, 10 mm thickness) of sodium iodide doped with thallium or other material efficiently emits a light photon upon interacting with a gamma ray. The light guide transfers light to a photomultiplier. The photomultiplier converts the light to an electrical pulse. Typically there is a dense array of photomultipliers attached to the light guide and crystal. The amount of light detected by any one photomultiplier is inversely related to the lateral distance of the light source to the center of the photomultiplier. Suppose a scintillation occurs midway between two photomultipliers from an array of 30, then equal signals will appear in these two photomultipliers. The others will get progressively less light the farther they are from the site of scintillation. In this way, the location (x,y) where the gamma ray entered the crystal can be calculated. These cameras can be positioned systematically to cover the entire body producing a complete whole-body projection. Such a device is termed a rectilinear camera because it follows straight lines systematically in a rectangular pattern over the body.

Computed tomography requires multiple projections at different angles (i.e., θ). To achieve this, a gamma camera needs to rotate around the body or multiple gamma cameras need to be placed around the body. In essence, this technology constitutes SPECT.

40.3.6.5. Imaging Principles

The term image quality refers to the fidelity of reproduction of whatever was imaged. Image quality is determined by its spatial resolution, contrast (difference in image intensity at a boundary), and noise. Spatial resolution refers to how sharp and detailed an image appears. Resolution is reflected in sharp boundaries, small pointed objects, etc. Sharpness depends on the ability to see two closely spaced features. *Spatial resolution* of an image is typically expressed by its full-width at half-maximum (FWHM). FWHM of an image is measured in units of space (e.g., mm). For a projection that has a normal distribution (e.g., projection of a point source), the FWHM is directly proportional to the standard deviation of the distribution. The significance of the FWHM concerns the ability to resolve two closely spaced features (e.g., point sources) in an image. Two features that are spaced apart less than the FWHM will not be resolved as two features, but rather as one blurred feature. If the features are further apart than the FWHM, then the peaks of the two normal distributions will be detectable, as the features will be resolved. The FWHM directly impacts upon the appearance of the image through a partial volume effect, which will be explained below.

The sampling theorem states that to recover spatial frequencies of an object up to a maximum of γ_{MAX} requires temporal sampling finer than $1(2 \times \gamma_{MAX})$. In other words, the highest frequency recovered must be sampled at least twice per cycle. Intrinsic *resolution* of the camera is the limit achievable based on the characteristics of the gamma detector and associated electronics. For example, thicker detector crystals cause worsening of the intrinsic resolution because the scintillation photons have a greater distance to spread before hitting the photomultiplier. In the imaging literature, the spatial resolution of the scanner is often confused with the image spatial resolution. Typically the image spatial resolution is worse than the intrinsic resolution because of counting statistics, reconstruction, and post-processing of images.

Closely related to spatial resolution is the partial volume effect. Ideally, the intensity of a voxel in the image should accurately reflect the amount of radioactivity in a similar volume in the patient. To achieve this, the resolution of the instrument must at least be able to resolve adjacent voxels. Otherwise, the two voxels will be blurred together resulting in an incorrect measurement of each voxel's activity. Images obtained from older scanners with low resolution mix activity from grey and white matter and CSF, to varying degrees produce a continuous range of activities when in reality only three activities are present (i.e., that for white and grey matter and CSF). If the instrument had high resolution, the grey and white matter and CSF would be clearly visible as in structural magnetic resonance imaging. Grey matter has four times as much blood flow or glucose metabolism as white matter, so the grey/white matter border should have clear contrast. CSF has no blood flow. Partial volume effects also occur in MRI when the size of the structure is less than the instrument's resolution. For example, if the resolution of the MRI scanner is 1 mm, then the signal from a 0.2 mm vessel will be averaged with signals from adjacent tissue and will not be seen clearly.

Another important characteristic of gamma cameras is the uniformity of the field of view. Uniformity means that the same amount of radioactivity in a sample will give the same counts no matter where the sample is placed inside the field of view. If a large cylinder is filled with an isotope dissolved in a solvent and mixed well, an image of the cylinder should be uniform throughout as long as self-attenuation is measured accurately.

40.3.6.6. Single Photon Emission Tomography

As reviewed above, the early application of gamma cameras was to obtain a 2-D projection of the organ under study. When the principles of tomography became clear, the gamma camera was adapted to permit computed tomography. The patient was injected with an isotope or radiotracer and the distribution of the isotope in the brain was imaged. Either one head (i.e., a gamma camera) or multiple heads could be rotated around the patient's brain. Then the images were created through reconstruction of the projection data. In this way, the gamma camera was transformed into a SPECT scanner.

SPECT had to deal with several technical issues. First, the weak link in SPECT is the use of a collimator to produce projections. It is assumed that a pinhole collimator's line of response reflects a cylinder. However, the lines of response actually span a diverging cone. The tissue right next to the collimator at the body's surface will be accurately projected onto the crystal and photomultiplier. However, tissue from deep inside the body will be projected over several collimator holes, therefore, will be localized less accurately. Second, it is assumed that the signal recorded is proportional to the total activity within a cylinder of tissue. In fact, the signal is biased more for areas closer to the camera and less from activity farther away in the center of the camera. Third, it is assumed that radioactivity outside the cylindrical line of response does not contribute to the observed signal. In reality, there is cross-talk between the lines of response due to scattered radiation. These issues directly impact SPECT images.

The use of collimators gives SPECT some problems. The instrument's sensitivity is decreased because much radiation is blocked by the collimator used to produce projections. Collimators also cause diminishing recovery of the radioactivity in areas further away from the detectors. Also, the resolution decreases with distance from the camera. Some of these problems

have only partial solutions. Therefore, in general, SPECT images are considered less quantitative and sensitive than those from PET. However, the increase in quantitation in PET comes at a large increase in cost. Many clinical procedures can be handled qualitatively.

The brain, skull, and scalp all decrease the radioactivity observed at the detectors. Therefore, imaging a hollow plastic cylinder filled with a uniform concentration of isotope (called a phantom) results in an artifactual decrease in the measured radioactivity at the center of the cylinder where the gamma rays need travel the most to reach the detectors. One way to perform *attenuation correction* is to calculate an attenuation map. A radioactive source with a long half-life (allowing repeated use across study sessions) such as a rod containing ^{153}Gd (half-life 242 days) moves over the detector array. The "blank scan" (B) is acquired in the presence of the radioactive rod without any object in the field of view. A "transmission" scan (T) is then obtained by putting the patient in the field of view and measuring the decrease in measured counts from that of the blank scan. Transmission scans measured this way look like poor quality CT scans. In fact, most modern scanners incorporate an X-ray source to obtain a CT to get an accurate attenuation correction as well as an anatomical picture. The measured attenuation scan can be used for attenuation correction assuming a constant attenuation coefficient. In reality, the passage through scalp, skull, and brain involves different attenuation coefficients making this approach only an approximation. In fact, PET's ability to overcome the attenuation correction problem makes PET more quantitative than SPECT and less susceptible to assumptions used to make corrections.

Another need is to correct for scattered radiation. Scatter correction is less in magnitude than attenuation correction. Scatter decreases image contrast and causes overestimation of the activity in a voxel. A variety of scatter correction methods have been used, but none is perfect.

The most widely used radioisotope for SPECT is 99mTechnitium (99mTc) that has a half-life of about 6 hours and emits gamma rays with 140 keV, an energy very favorable to SPECT imaging. The isotope can readily be made in the hospital setting by using a 99mTc generator kit that gets delivered on a weekly basis. Such a generator has parent-daughter atoms (e.g., ^{9}9mMo/99mTc) in a kit that permits isolation of the daughter for injection into the patient. The daughter is replenished continuously by radioactive decay of the parent. Depending upon the molecule attached to 99mTc, this radiotracer can be used in a variety of applications. For example, 99mTc-sestamibi is used routinely in the clinical setting for the assessment of myocardial perfusion. Assessment of cerebral perfusion uses 99mTc-HMPAO (hexamethylpropylene-amine oxime) or ^{99}mTc-ECD (N,N'-1,2-ethylenediyl-bis-L-cysteine diethylester). In medical centers without ^{18}F-fluorodeoxyglucose PET (FDG PET), 99mTc-HMPAO is used since brain perfusion is coupled to brain metabolism.

SPECT has several advantages including lower cost, greater availability, and convenient radiotracer generation. For example, if a patient has a seizure, the 99mTc-HMPAO can be quickly injected. The long half-life of this isotope permits the patient to receive the radiotracer injection at one location and still have time to travel to another location for the SPECT scanning. Likewise, brain perfusion imaging is possible during different stages of sleep by injecting 99mTc-HMPAO through a venous catheter at a time when electroencephalographic criteria are met without awakening the patient. After the label gets trapped in the brain according to blood flow, the patient can be awakened and transported to an imaging center for SPECT. The logistics of a similar study with ^{18}F-FDG PET are more difficult and demanding.

SPECT is used in studies of brain receptors, neurotransmitters, and other molecules relevant to psychiatry (155). Unlike in vitro ligand binding assays where the receptor dissociation constant (Kd, a measure of the affinity, 1/Kd, of the receptor for the ligand) and total receptor concentration (Bmax) can be individually determined through a Scatchard type analysis, SPECT receptor assays typically only determine the *binding potential*, a hybrid measure which is Bmax/Kd. This measure is akin to the net drive to bind ligand (related to total number of receptors and the affinity of the receptor for the ligand), but does complicate the traditional pharmacological interpretations of receptor ligand interactions. The reason for this problem is that usually one cannot administer high concentrations of cold ligand to displace 50% of the radiotracer—the usual way to measure Bmax and Kd in vitro. Less often, two modifications are used to obtain the true Bmax and Kd.

The first modification is a multi-injection protocol (156, 157). The first injection uses only the radiotracer at high specific activity where receptor occupancy is almost zero. Then a prolonged constant infusion of cold ligand is designed to achieve steady state at about 50% receptor occupancy. After steady state is achieved in 1–2 hours, the high specific activity radiotracer is injected again. These two scans in essence provide the minimal two points (0% occupancy and 50% occupancy) for a Scathard analysis without violating steady state assumptions.

Alternatively, a dual-ligand protocol can be used if an antagonist of the receptor lacks pharmacologic activity, thereby permitting the use of high concentrations to displace the radiotracer without concern of toxicity for the subject (158). Absolute quantitation is not as important as the relative value because the binding constant derives from the concentration of cold ligand producing a 50% decrease in tracer binding. These types of studies minimize the impact of SPECT's approximate corrections for attenuation and scatter.

Recent years have seen the combination of SPECT and CT into one device enabling coregistered acquisition of the radiotracer distribution as well as anatomy. This arrangement helps improve attenuation correction because the CT scans have far more detail than the transmission scans obtained with SPECT rods or other emission device. In the future, combination of SPECT and MRI may also become available.

40.3.6.7. Positron Emission Tomography (PET)

40.3.6.7.1. Tracer Production

Most positron emitting radiotracers are made in a cyclotron. Ernest O. Lawrence conceived of the cyclotron principle in 1929 (1901–1958). He, along with M.S. Livingston, built the first successful model in 1931. He was awarded the Nobel Prize in 1939 for the invention. A cyclotron consists of a powerful magnet; a vacuum chamber containing two back-to-back D-shaped hollow electrode tubes called "dees," each separated from one another by a gap; a high frequency oscillator connected to the two dees; an ion source; and a target. The ion source in the gap at the center of the two half cylinder dees generates charged particles by passing an electric discharge through a gas. These particles are in an electric field because the two dees have an electric potential between them. The particle thus accelerates until entry into the opposing dee where there is no electric field. Here, the particle's path becomes circular because of the right-hand rule and the magnetic field oriented perpendicular to the dees. Upon approaching the gap again, the electric field changes in the opposite direction, and the particle is once again accelerated into the opposing dee. As the particle accelerates, it increases energy, and therefore, the radius expands until the particle is directed with high energy (10–40 meV) into a target that contains the substrates for the nuclear reaction. For example, to make ^{18}F to label FDG, the target is filled with ^{18}O-oxygen (present naturally in 0.2% abundance). In this case, a proton smashes the oxygen nucleus which gains a proton, then loses a neutrino, becoming ^{18}F (no change in mass; increase of 1 proton). Subsequently, during positron decay, ^{18}F loses a proton by ejecting a positron and a neutrino to become ^{18}O.

40.3.6.7.2. Positron Emission

Positron emission involves the loss of a proton (and transmutation of the element to the left on the periodic table), and the ejection of a neutrino and positron. The positron travels a short distance to combine with an electron to get annihilated with the emission of two gamma rays each with 511 keV traveling approximately 180 degrees apart. The distance the positron travels before annihilation depends on its energy and is termed the positron range. Therefore, a point source of ^{15}O (maximal energy 1720 keV) appears more blurry given its greater positron range than ^{18}F (maximal energy 635 keV). The positron range places a theoretical limit on the ultimate resolution of PET. Some of the commonly used positron emitters of interest in medicine are listed in Table 40.4; positron decay is denoted as $\beta+$.

ORISE (Oak Ridge Institute for Science and Education) has published effective dose equivalents for the various organ systems and different radiotracers. The calculation of the radiation dose to a target organ from one or more source organs is termed dosimetry. The usual method is termed absorbed fraction dosimetry which was established by MIRD (Medical Internal Radiation Dosimetry) committee. This estimate of radiation dose needs to be calculated for the proposed dose to ensure the exposure is within FDA limits for research.

Since SPECT is essentially a gamma camera, why not use a PET camera to image radiopharmaceuticals that emit only a single photon? PET cameras are not equipped with mechanical collimators. Also, the differences in energy between SPECT and PET gamma emissions (PET>SPECT) means that the PET instrument is not engineered optimally to detect SPECT's lower energy emissions. Of course, both technologies rely on photomultipliers to convert the scintillations into electric pulses.

TABLE 40.4. Common positron emitting isotopes in medicine.

Some positron-emitting nuclides used for in vivo imaging				
Radionuclide	Half-life	β^+ fraction	Maximum e^+ energy	How produced
^{11}C	20.4 minutes	0.99	960 keV	Cyclotron
^{13}N	9.96 minutes	1.0	1.19 MeV	Cyclotron
^{15}O	123 seconds	1.0	1.72 MeV	Cyclotron
^{18}F	110 minutes	0.97	635 keV	Cyclotron
^{62}Cu	9.74 minutes	0.98	2.94 MeV	Generator (from ^{62}Zn)
^{64}Cu	12.7 hours	0.19	580 keV	Cyclotron
^{68}Ga	68.3 minutes	0.88	1.9 MeV	Generator (from ^{68}Ge)
^{76}Br	16.1 hour	0.54	3.7 MeV	Cyclotron
^{82}Rb	78 seconds	0.95	3.35 MeV	Generator (from ^{82}Sr)
^{124}I	4.18 days	0.22	1.5 MeV	Cyclotron

40.3.6.7.3. Reconstruction

PET has some advantages over SPECT. The nearly precise 180 degree alignment of the two annihilation gamma rays permits a type of electronic collimation avoiding the use of mechanical collimators and, thus, vastly increasing sensitivity. Electronic collimation arises when the two annihilation gamma rays hit opposite PET detectors almost simultaneously (i.e., within fractions of a nanosecond). Therefore, the annihilation occurs along the line of response traced by the two detectors. Taking all possible lines of response and using tomographic methods, as discussed above, an image of the radiotracer is produced. Either filtered back-projection or iterative algorithms are used for reconstruction. SPECT has the problem of varying resolution and radiation recovery with respect to the distance to the gamma camera. PET has the property that both recovery and resolution do not change with depth, thereby avoiding the partial corrections used in SPECT.

The largest correction in PET, as in SPECT, is attenuation correction: correcting for the absorption of the emitted gamma rays with passage through brain, bone, and scalp. Fortuitously, PET has the property that attenuation can be accurately measured without approximations and other assumptions. This arises by performing a "blank" scan (nothing in the field of view) and a "transmission" scan (with the head in the field of view). Previously, a rotating rod or cylinder containing radioactive material was passed over all detectors, and the decrease in counts with the patient in the scanner was compared to the blank scan permitting accurate calculation of the attenuation. Increasingly, PET/CT systems are becoming available. These systems use the CT scan to measure attenuation correction.

Additional corrections in PET arise because of random and scattered radiation. *True coincidences* are those detected by two detectors that arise from an actual annihilation event along the line of response. *Scatter coincidences* occur when one or both gamma rays are bent through scatter by interaction with the body and then deviate from the near perfect 180 degree alignment. Thus two detectors may be hit by the gamma rays simultaneously, yet the apparent line of response does not pass through the annihilation event. *Random coincidences* (also called accidental coincidences) occur when the gamma rays from two different annihilation events happen to hit two detectors within the same time or coincidence window. These two hits are considered "simultaneous"; however, the gamma rays did not come from one annihilation event. The random coincidences increase as the amount of radioactivity in the field of view increases. There are formulas to correct for random coincidence events.

40.3.6.7.4. Instrumentation

The first positron device was invented in 1951 independently by two groups: William H. Sweet (159) of Massachusetts General Hospital, and Phillip Handler (160) at Duke University. These devices consisted of two sodium iodide detectors situated oppositely and used mechanical collimation. The earliest applications were in neurosurgery to detect cerebral neoplasms. After the development of computed tomography by Hounsfield, a group at Washington University led by Michele Ter-Pogossian, saw the great potential of applying this early technology for non-invasive imaging in humans. The first multi-crystal scanner was invented in 1975 by Drs. Ter-Pogossian, Phelps, and Hoffman (161, 162). Thereafter, progressively greater number of detectors and multiple rings of detectors brought the technology to maturity. Improvements in crystal technology led to the more sensitive, crystal material called lutetium orthosilicate (LSO). In addition, sensitivity was greatly improved by using fully 3-D imaging without the use of septae between rings of different slices thereby increasing sensitivity.

Several additional technical developments in instrumentation have provided for recent innovations. Micro PET machines have been developed for imaging of small animals with application to preclinical studies. The capability of sub-nanosecond timing allows estimation of the location of the annihilation along the line of response leading to "time of flight" PET with additional spatial resolution. Modern PET scanners have 2 mm isotropic resolution. In addition to PET/CT, PET/MRI machines are coming to market. The capability of PET/MRI machines to achieve quantitative attenuation correction based upon the MRI image is an area of active investigation. In addition, PET/MRI systems are also in the early phases of implementation. However, the quantitation of attenuation based upon the MRI remains in development and under optimization.

40.3.6.7.5. Applications of PET

The clinical application of molecular imaging to the differential diagnosis of dementia serves as a roadmap for combining standard clinical and neuropsychological testing with the unique information from neuroimaging and neuroinformatics to directly impact patient care. For various types of dementia, ^{18}F-FDG PET neuroimaging is indicated when, despite first-line evaluations such as laboratory studies and MRI, the differential diagnosis between Alzheimer's disease and frontotemporal dementia remains unclear. Both federal and private insurance carriers will generally reimburse for this indication.

The FDA has recently cleared amyloid imaging, specifically with ^{18}F-Florbetapir PET, after studies demonstrated that antemortem amyloid ^{18}F-Florbetapir PET scans showed high correlations with postmortem histopathology for amyloid

plaques (163). The interpretation of a positive amyloid PET scan in otherwise healthy elders (i.e., without gross cognitive decline) remains unclear and is under active investigation. Recently, the Society of Nuclear Medicine and Molecular Imaging and the Alzheimer's Association published criteria for appropriate clinical use of amyloid imaging (164). However, insurance carriers have for the most part (as of 2014) denied reimbursement for amyloid PET imaging under most indications.

40.3.6.7.6. Tracer Kinetic Modeling

SPECT and PET provide tools to measure the amount of a radioactive substance in the brain non-invasively at a given point in time using emission computed tomography. However, measurement of a quantity does not translate directly into the measurement of a physiological process. The process of converting a measured amount of radioactivity as a function of time into a measure of physiology requires *tracer kinetic modeling*. First, the physiological process under inquiry requires definition. Such processes can for example be brain blood flow, brain glucose metabolism, receptor-ligand binding, protein synthesis, lipid synthesis, gene expression, etc. A radiotracer needs to be selected that will probe the physiological process. For example, radiolabeled water or butanol, almost freely diffusible, are used to measure brain blood flow. Fluorodeoxyglucose, fluorine substituting for the hydroxyl group on the second carbon of glucose, is a competitive substrate with glucose for carrier-mediated diffusion mechanism into the brain. In the brain and elsewhere in the body, the fluorodeoxyglucose is phosphorylated by hexokinase. Once the FDG is phosphorylated by hexokinase, it becomes trapped and cannot undergo further metabolism. Therefore, the uptake and trapping of FDG is a good measure of glucose metabolism. This tracer is among PET's, most frequently used procedure. The method was developed by Louis Sokoloff at the NIH (165, 166). Second, the number and types of compartments must be established. A compartment is an idealized volume or space within which a tracer becomes instantaneously and uniformly distributed, i.e., without concentration gradients. For example, Sokoloff's three-compartment model for FDG determination of glucose metabolism has the three compartments: vascular compartment, the "free" compartment where FDG is in the tissue but not phosphorylated, and a metabolic compartment where the glucose or FDG is trapped. Third, the kinetics of movement between components needs assignment. In most models, first-order rate constants describe flux of material across compartments. For example, in a simple two compartment model (A, B) each having concentration C_A and C_B with first-order rate constants k_1 and k_2, respectively:

$dC_B(t)/dt$ = flux into compartment B from compartment A minus flux out of compartment B into compartment A = $k_1C_A - k_2C_B$.

Using a model and appropriate measurement of kinetics, the radioactivity measurement obtained from SPECT or PET can be converted into a quantitative physiological parameter.

40.3.6.7.7. Brain Blood Flow

The development and application of neuroimaging arose from work by pioneers in psychiatry in their search for answers to questions about consciousness and disorders of the mind. Seymour S. Kety (1915–2000), although neither a psychiatrist nor a neurologist (167), realized the importance of quantitative measurement of brain blood flow and metabolism to study the mind:

"But to me, the most interesting information contained in the table [Table 40.5] is the finding that in a large group of mental states markedly different from normal, there is no significant deviation in cerebral oxygen consumption (167)."

He, in collaboration with Carl Schmidt, pioneered the measurement of brain blood flow based upon the Fick Principle (168): the quantity of a substance taken up by the brain during time T (mole/min/kg tissue) is the time integral of the difference between the arterial (carotid artery) and venous (internal jugular bulb) concentrations (mole/l) multiplied by the brain blood flow (l/min/kg tissue). Kety reasoned that a freely diffusible inert tracer such as N_2O could be used. Then, deriving

TABLE 40.5. Mental states and associated oxygen consumption.

Brain state	Oxygen consumption (%of normal)
Normal Sleep	97%
Schizophrenia	100%
LSD Psychosis	101%
Mental arithmetic	102%
Anxiety	118%
Epinephrine infusion	122%
Alcoholic coma	49%
Hypothermia	67%
Surgical anaesthesia	64%

From Kety SS. A biologist examines the mind and behavior. Science 1960;132:1861–1867. Reprinted with permission from AAAS.

several dependent measures permits calculation of cerebral blood flow (CBF). Kety's required measures to calculate CBF were: N_2O concentration difference between arterial (A) and venous (V) samples over time, $\Delta AV(t)$(mole/l); brain volume V (1); and brain weight W (kg). At equilibrium, the amount of tracer taken up by the brain, ΔN_2O is simply the partition coefficient of the tracer, S, times the brain volume V. Thus, $CBF = VS/\int \Delta AV(t)dt$. An autoradiogram using a radioactive tracer and this technique allows the sharp contrast in blood flow between grey and white matter to be clearly visible. This work presaged the future development of techniques permitting non-invasive autoradiography in humans using computed tomography.

In 1983, Huang et al. (169) and Raichle et al. (170, 171) published non-invasive methods to measure CBF in humans using PET and the almost freely diffusible tracer, ^{15}O-labeled water. In their most quantitative form, arterial blood sampling was required. However, Fox et al. (172) soon thereafter showed that if global brain blood flow did not significantly change, as occurs with most cognitive tasks, an estimate of rCBF could be made by using an intravenous bolus injection of radiolabeled water and measuring the integrated radioactivity over 40 seconds (provided directly by the PET scanner) after the initial entry of the tracer into the brain. In essence, using a short time interval captures the entry of the tracer into the brain before it has a chance to leave the brain and recirculate. The use of normalized tissue counts as a proxy for brain activity provided the breakthrough to measure neuronal activity in the brain easily and efficiently. Additionally, the use of image averaging and cognitive neuroscience techniques paved the way for routine brain mapping studies to localize basic cognitive operations in humans (173). The bolus autoradiographic PET techniques for cognitive activation studies had several key advantages. Multiple "snapshots" of brain blood flow in different cognitive states (up to 12 per study session lasting about 2 hours) became routine. Differences between images enabled isolation of the cognitive process under study. The short half-life of ^{15}O-labelled water (~2 minutes) meant 10 minutes after a snapshot, another scan was possible. Additionally, the brief imaging period (40 seconds; neurovascular response time, 6–10 seconds) minimized habituation and learning effects during the actual scan.

40.3.6.7.8. Brain Glucose Metabolism

Along with the development of methods for measuring CBF, Louis Sokoloff and colleagues developed the deoxyglucose technique (164, 165). The basic principles were reviewed above. Glucose provides 95–99% of the brain's energy under normal physiologic conditions. In fact, the brain is the largest consumer of blood glucose. The rate of glucose utilization is an excellent indicator of energy requiring functions of the brain such as neuronal activity which requires maintenance of membrane potentials, large ionic fluxes, metabolite shuttles, neurotransmitter synthesis, vesicular transport, etc. To study disease and the effects of treatment, the FDG technique became essential because the coupling of flow and metabolism can be dissociated by disease or altered by medications that affect the neurovasculature. FDG directly measures neuronal metabolism and, therefore, is not subject to these problems.

The technique involves an intravenous injection of ^{18}F-FDG into a subject who has been fasting to avoid postprandial elevation of glucose which would compete with FDG. In turn, this means that special modifications of the method are required when measuring brain glucose metabolism in diabetic patients. For absolute quantitation, the arterial blood must be sampled to measure the ^{18}F-FDG concentration over time. Additional measures include the plasma glucose concentration and several constants that can be derived from the published literature. Typically, the subject's mental state is held constant over 40 minutes while steady state is reached. The method is most sensitive to the metabolic activity of the brain over the first 15–20 minutes. A scan is then obtained which measures the distribution of the trapped ^{18}F-FDG. The rCMRglu is calculated for each voxel in the image or each region of interest. In psychiatry, there has been much debate about the optimal state under which the subject should be studied. Frequently, the state is resting with eyes closed or with eyes focused upon a small central fixation stimulus. At first impression, these simple task conditions may seem very uncontrolled, but in actual fact, these control task states are quite reproducible and each may be reflecting a default-mode, idling state, which may be useful to employ when comparing baseline functional activity across clinical groups (174). Some groups also use an easy vigilance type of task, such as the continuous performance task (CPT) as a standard task. Needless to say, the specific task does affect the results. This is an important component of the methods section in the research report.

As in measurement of rCBF, the method can be simplified greatly if absolute quantitation is not needed, but rather, relative regional glucose metabolism is acceptable. Using this approach, no arterial sampling nor measurement of plasma glucose concentration is needed. The accumulated whole-brain radioactivity in a 10–20 minute scan is normalized to a fixed value to account for slight differences in injected radioactivity or inter-subject differences in whole brain metabolism. Thus, the scan directly displays the relative rCMRglu without further calculations. It is important to note that the relative and absolute measures can produce different results and different patterns of distribution of metabolism.

Relative or absolute measurement of brain glucose metabolism is the usual method used to characterize alterations in brain function associated with psychiatric disease. The method has higher resolution than rCBF methods, greater signal-to-noise (the longer half-life of 2 hours permits more prolonged scanning at higher count rates, thereby improving imaging statistics),

and, as mentioned previously, can be used in the presence of medications that alter the flow properties of the vasculature. Therefore, this method is also used to map the metabolic effects of medications in defining mechanisms of action as long as blood flow is not a major contributor to the physiology.

40.3.6.7.9. Molecular Imaging and Molecular Medicine

The use of SPECT and particularly PET, because of increased sensitivity and potential for absolute quantitation, provides almost limitless potential to study biomolecules such as receptors, neurotransmitters, toxins, enzymes, and genes. Key issues are the process to study, the molecules involved, the radiotracer that will probe the molecules, and the tracer kinetic modeling that can translate the observed emission into a physiologically meaningful quantity.

Some of the radiotracers used in psychiatric studies are listed in Table 40.6. Perhaps among the most studied systems with relevance to psychiatry include probes of the dopamine and serotonin systems. These studies have provided among the first vistas of pathophysiology in neuropsychiatry.

TABLE 40.6. Radiotracers used in psychiatry.

Ligand	Modality	Target
[^{11}C]DASB	PET	SERT
[^{11}C]ADAM	PET	SERT
[^{11}C]NNC-112	PET	D1R
[^{11}C]SCH23390	PET	D1R
[^{11}C]FLB457	PET	D2R
[^{11}C] raclopride	PET	D2R
[^{18}F]fallypride	PET	D2R
[^{123}I]IBZM	SPECT	D2R
[^{11}C]NPA	PET	D2R
[^{123}I]epidepride	SPECT	D2R
[^{18}F]fluorodopa	PET	Presynaptic marker
[^{99m}Tc] TRODAT	SPECT	DAT
[^{11}C]methylphenidate	PET	DAT
[^{11}C]cocaine	PET	DAT
[^{123}I]3ocai	SPECT	DAT
[^{11}C] WIN 35428	PET	DAT
[^{18}F]FECNT	PET	DAT
[^{11}C]DTBZ	PET	VMAT2
[^{18}F]-AV-133	PET	VMAT2
[^{18}F]FDDNP	PET	Amyloid
[^{11}C]PIB	PET	Amyloid
[^{11}C]SB-13	PET	Amyloid
[^{123}I]iomazenil	SPECT	GABA-AR
[^{11}C]RO 15 1788	PET	GABA-AR
[^{11}C]flumazenil	PET	GABA-AR
(S,S)-[^{18}F]FMeNER-D2	PET	NET
[^{11}C]nomifensin	PET	NET
[^{123}I]5-I-A-85380	SPECT	αPECT-A-85
[^{11}C]ABP688	PET	mGluR5
[^{18}F]SP203	PET	mGluR5
[^{11}C]JNJ42491293	PET	mGluR2
[^{18}F-deuteroaltanserin	PET	5HT2aR
^{18}F]altanserin	PET	5HT2aR
[^{18}F]ketanserin	PET	5HT2aR
[1^{8} F]Setoperone	PET	5HT2aR
[carbonyl-(11)C]WAY-100635	PET	5HT1AR
[^{11}C]carfentanil	PET	METartfent
[^{11}C]deprenyl	PET	MAO-B
[^{18}F]FEPPA	PET	TSPO
[^{11}C]PBR28	PET	TSPO
[^{11}C]clorgyline	PET	MAO-A

Dopaminergic modulation of both normal and pathophysiological states has been demonstrated using a variety of approaches. A correlation with the number of dopamine receptors and measures of novelty seeking in healthy subjects suggests an important role of tonic dopamine release in aspects of personality (175). Investigators have measured in healthy subjects both fMRI BOLD activation and displacement of tracer from dopamine D2 receptors. Increased activation of the substantia nigra/ventral tegmental region (the principal origin of mesolimbic dopamine neurotransmission), as well as its principal targets (ventral striatum, amygdala, and hippocampus) correlated with reward-related dopamine release (176). In schizophrenia, measurement of decreased density of dopamine D2 receptor following administration of amphetamine, correlating with positive psychotic symptoms, indicates an important role of exaggerated dopaminergic neurotransmission in psychosis (177). Measurement of D2 receptor occupancy indicates that 2/3 occupancy by antipsychotic is required for acute improvement in symptoms of schizophrenia, while greater occupancy is associated with hyperprolactinemia and extrapyramidal side effects (178, 179). A recent review posits that the principal abnormality in schizophrenia arises from presynaptic dysregulation as measured with L-dopa and other probes of presynaptic dopamine (180).

Multimodal approaches offer particular promise. Aside from dopamine studies cited above, PET has been combined with fMRI to examine serotoninergic neuromodulation. In one such study (181), PET was used to measure 5HT1A autoreceptor binding in the raphé, nucleus, which secretes serotonin into the amygdala, while fMRI was used to measure amygdala reactivity to face stimuli using BOLD. They found a reduction in inhibitory 5HT1A autoreceptors in the raphé, i.e. diminished capacity for autoinhibition of serotonin release was correlated with increased amygdala reactivity to visual stimulation. In other words, a simplistic interpretation is that serotonin levels in the raphé were less effective at inhibiting raphé neuron firing. In turn, a relative excess of serotonin in the amygdala would increase its reactivity to affective stimuli. Of note, postsynaptic 5HT1A binding in the amygdala explained little of the variance. Furthermore, mouse knock-outs of the 5HT1A receptors lead to an anxiety-like syndrome (182). Such work begins to identify neuromodulatory mechanisms at the level of systems neuroscience. This research bears directly upon how such systems become dysregulated in depression.

Recent work suggests that in the near future, the level of gene expression in the human brain will be measured quantitatively permitting understanding of gene regulation and its interaction with the environment. The initial studies were done using MRI and iron-labeled oligodeoxynucleotides complementary to the gene of interest (183). In this study, an oligonucleotide complementary to the mRNA of c-Fos, a marker of neuronal activation, was coupled to superparamagnetic iron oxide nanoparticles that are a T2* contrast agent. This probe was retained in cells as visualized with iron histochemistry which correlated nicely with the change in MR signal. In proof of concept, Liu et al. (183) demonstrated in live rats using MRI, increased binding of the probe following injection of amphetamine in the nucleus accumbens, medial prefrontal cortex, and striatum—all structures known to activate (increased c-*fos* protein and *c-fos* mRNA) in response to this drug. Although demonstrated using MRI, use of PET radioligands has the potential for even greater sensitivity (184). Such technology portends that in vivo, non-invasive, imaging of human gene expression is possible in the not too distant future. This ability will be particularly important in psychiatry where diseases have complex genetics with strong environmental effects thereby modulating gene expression.

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Free Resources

http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/ illustrates some of the data analysis tools for the magnetic resonance techniques.

http://en.wikipedia.org/wiki/Magnetoencephalography details the basic aspects of magnetoencephalography, including photo of a neuromagnetometer.

http://en.wikipedia.org/wiki/Positron_emission_tomography describes the components and uses of positron emission tomography.

http://neuroimage.usc.edu/brainstorm illustrates data analysis software tools for neurophysiological data (MEG; EEG, etc).

http://www.fil.ion.ucl.ac.uk/spm/ offers data analysis software for neurophysiological data (EEG; MEG) and for tomographic neuroimaging data (PET, fMRI).

http://www.imaginggenetics.uci.edu/archive.asp demonstrates the added value of combining genetic information to neuroimaging/neurophysiological information to understand psychiatric disease, offers free lectures and slides from past meetings.

http://www.nmr.mgh.harvard.edu/martinos/research/technologies.php offers some of the applications for several neuroimaging technologies.

41
Electroconvulsive Therapy: Indications, Use and Adverse Effects

Suck Won Kim, M.D. and Jon E. Grant, M.D., J.D., M.P.H.

Abstract In this chapter, we discuss indications, pre-ECT evaluations, concurrent use of ECT and psychotropic medications, right unilateral ultra-brief pulse wave ECT, methods of ECT administration, adverse reactions, methods of management for those who fail to respond to the index ECT treatment, continuation of ECT and maintenance of ECT. Primary focus is for those psychiatrists who refer their patients to an ECT specialist. A brief summary for the newly emerging right unilateral ultra-brief pulse width ECT has been incorporated.

Keywords ECT • Ultra brief unilateral pulse width • Refractory depression

41.1. Introduction

Primary goal of this chapter is to summarize clinical indications, method of applications and unwanted consequences of ECT for those psychiatrists who refer their patients to ECT specialists. The most comprehensive book on ECT is the Practice of Electroconvulsive Therapy by the American Psychiatric Association (1). The information compiled in this book chapter depended, in part, on the above book, books by Maletzky (2), Fink (3), Abrams (4) and also based on over 40 years of clinical experience of administering ECT by the first author.

ECT used to be used by most practicing psychiatrists but recently the trend has been that a good number of psychiatrists refer their patients to specialists with ECT training and experience. Many years ago, psychiatrists used to be in charge of induction procedure, administration and recovery from ECT. Nowadays, the procedure is, in most cases, performed in an ECT preparatory room where I.V. is established and pre-ECT medications are administered; ECT administration room where an anesthesiologist is in charge of general anesthesia and a psychiatrist administers ECT; and recovery room where nurses provide services during the recovery phase from anesthesia. Typically, ECT is administered three times a week for a total of eight treatments. With an advent of ultra-brief pulse width unilateral ECT the average treatment number is likely to increase. Unless future research findings suggest otherwise the ultra-brief pulse width right unilateral ECT is likely to dominate future ECT (5–12). This is primarily because of a dramatic reduction in memory loss with the ultra-brief pulse width ECT technique.

In the past ECT was given only to an inpatient. Although outpatient ECT is not new, during the past decade an increasing number of patients have been given outpatient ECT and the trend indicates that the number will increase further in the future. Most often, outpatient ECT is administered twice a month. Outpatient ECT can be arranged from the beginning of ECT or

S.W. Kim, M.D. (✉)
Professor, Department of Psychiatry, University of Minnesota Medical School, Minneapolis, MN, USA
e-mail: kimxx003@umn.edu

J.E. Grant, M.D., J.D., M.P.H.
Professor, Department of Psychiatry and Behavioral Neuroscience, University of Chicago Pritzker School of Medicine, Chicago, IL, USA
e-mail: jgrant4@bsd.uchicago.edu

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after a partial completion or full completion of a series of ECT in the case of an inpatient. In the latter case, three times a week ECT is extended to once a week for two to four weeks then the interval of ECT is lengthened to every other week to once a month. The patient often can pinpoint as to how long the effect of each ECT lasts and the clinician often sets the ECT interval based on such a report and other relevant clinical information.

Successful outpatient ECT often requires cooperation by family members, ECT scheduling staff and the psychiatrist. This is especially so because there are no trained personnel at home who can professionally supervise or observe the patient as is the case for an inpatient. Recently, the specific timing of outpatient ECT has been reviewed by Petrides (13).

Clinicians have been administering outpatient ECT for many years and clinical safety for a long-term (not clearly defined) outpatient ECT is reasonably well established and empirical data for the safety of long-term ECT are now found in the literature (14–16). Wachtel and colleagues reported the stability of neuropsychologic testing in a 16-year-old boy with cerebellar dysgenesis who received 61 acute and maintenance electroconvulsive therapy treatments for malignant catatonia (14). Trevino and colleagues reviewed the literature and found the risk and severity of cognitive impairment low (15). Martínez-Amorós and colleagues, in a comprehensive review paper summarized that maintenance ECT is safe and effective (16).

In general, it is true that ECT is safe and effective, however, a psychiatrist who is to recommend ECT to his or her patient should not over-emphasize the safety or efficacy of ECT; failure rate of ECT is not small (6) and cardiac and other clinically significant complications do occur with ECT.

41.2. Indications

There are psychiatrists who recommend ECT before commonly used treatments have all been tried. Others recommend ECT only as a last resort. One of the most common practices is that most psychiatrists recommend ECT before a trial with clomipramine or a monoamine oxidase inhibitor (MAOI). Approximately 50% of treatment refractory patients (especially the early stage refractory patients) respond to one of the MAOIs (18). We strongly recommend that psychiatrists try at least two MAOIs before recommending a patient for a series of ECT.

In treating patients with refractory depression a psychiatrist should not adhere only to those compounds with which they feel comfortable. This means that he or she will apply all known selective serotonin reuptake inhibitors (SSRIs) one by one, venlafaxine, bupropion, mirtazapine, duloxetine or trazodone yet never use clomipramine or an MAOI. What this often means is that the patient goes through a few to several years without feeling any relief from his or her depression.

For suicidal patients, ECT can be a life-saving measure. Selected catatonic cases also respond well to ECT.

ECT should be considered for patients with treatment refractory depression, psychotic depression, mania, schizophreniform disorder, schizoaffective disorder and selected catatonia. Patients who have uncontrollable aggressive behavior, often accompanied by mental retardation, may respond to ECT. ECT has also been used for severe behavior problems associated with dementia. ECT has powerful anticonvulsant effects and has been used for intractable seizure disorders (19, 20).

41.3. Pre-ECT Evaluation

A comprehensive medical and psychiatric history is required to insure that there is a clear indication for ECT and ECT can be administered safely. Safety of anesthesia needs to be established. Although rare, there are patients who have a family history of pseudocholinesterase deficiency. These patients require a nondepolarizing muscle relaxant such as rocuronium or a related compound (21).

Often cardiology consultation is requested in the case of preexisting heart disease, in part, because of the known complications of ECT in patients with pre-existing heart disease. In a study, Zielinski and his colleagues reported that in the patients with pre-existing cardiovascular disease (n = 40) 15 developed ventricular arrhythmias, 9 developed ischemic events, 6 developed atrial arrhythmias and 3 developed bradycardias. In the same study, 8 patients developed persistent EKG changes accompanied by chest pain, asystole, or persistent arrhythmias (22).

Presence or absence of medical devices needs to be checked. Implanted cardiac pacemakers are often set to a fixed mode (by a magnet) from a demand mode. For those patients who have implanted cardiac defibrillators a cardiac electrophysiologist should be consulted to determine whether the function should be inhibited at the time of ECT. Patients with uncomplicated cardiac transplant do not present specific cardiac risk. A magnet is used for those patients with vagus nerve stimulator. ECT has been successfully used in a 68 year old woman with a deep brain stimulator implant (23). Her stimulator was turned off during ECT.

Pulmonary diseases are also examined closely because of the complications associated with anesthesia. Patients with excessive weight, sleep apnea or other airway abnormality need to be evaluated closely. Complete blood count and chemistry with sodium and potassium levels are routinely obtained. It used to be that spinal X-Ray and EEG were routinely obtained but nowadays these or head CT and MRI are obtained only when clinically indicated. Anticonvulsants, benzodiazepines or other seizure threshold raising drugs need to be tapered or discontinued before the first ECT. Dental status needs to be checked for presence of loose teeth, denture and other oral cavity problems. The ECT induced jaw tightening can damage the tongue. Dentures should be removed prior to ECT.

41.4. Concurrent Use of ECT and Psychotropic Medications

Lithium: Although there are reports that suggest that use of lithium is safe in ECT (24) there are many more study reports that suggest that there is a higher risk of delirium and CNS toxicity (25, 26). There may be patients who must stay on a small amount of lithium during ECT. Other than these unusual cases lithium should be discontinued before initiating ECT.

Anesthesia and MAOI can pose a serious clinical problem. If a pressor agent becomes necessary, in the presence of hypotension, there is a risk of precipitating hypertensive crisis in the presence of MAOI. Some clinicians do allow an MAOI during ECT if clinically justified.

Anticonvulsants and benzodiazepines should be tapered and discontinued. If a benzodiazepine has to be used it is generally withheld the night before ECT. Antipsychotics and antidepressants are commonly continued during ECT.

41.5. Method of ECT Administration

41.5.1. Right Unilateral Ultra-Brief Pulse Width ECT

Bitemporal electrode placement is still widely used. Advantages and disadvantages of bilateral vs. unilateral ECT have also been published extensively (27, 28). Although it would be more appropriate to describe the subject comprehensively, in this chapter we focus only on the right unilateral ultra-brief pulse wave width ECT. There is a dramatic reduction in memory loss seen with this new treatment.

The severity of cognitive impairment after ECT is, at least in part, associated with the amount of energy needed to induce a seizure. Reduction of the pulse width of the electrical current to induce seizures in ECT—from brief pulse (BP) (0.5 ms and up) to ultrabrief pulse (UBP) (0.2–0.3 ms pulse width)—may minimize cognitive impairment while maintaining efficacy (29). By using a narrower pulse-width, ultra-brief pulse ECT appears to stimulate a smaller band of tissue, minimizing stimulation of adjacent, non-targeted brain areas, and thus reducing associated side-effects. Analysis of cognitive outcomes in patients treated with ultrabrief pulse width has demonstrated significantly less impairment of anterograde and retrograde memory compared to patients receiving standard pulse width stimulation (30). Sackeim and his colleagues have summarized cognitive and affective consequences of right unilateral ultra-brief pulse width ECT (31, 32). They noted that ultra-brief stimulation is more efficient in seizure induction and found that memory loss was dramatically reduced when compared to the standard pulse width stimulation.

As usual, we have had difficulty inducing or maintaining seizures in some cases. In such cases, we use hyperventilation, I.V. caffeine and/or an alternative anesthetic such as etomidate (33). In contrast to barbiturate class of drugs such as thiopental or methohexital, etomidate does not raise seizure threshold. Etomidate, however, is known to cause reversible adrenal suppression (34) and should not be used routinely.

Technical aspects of ECT administration have not been addressed in this chapter. Interested readers need to refer to the Practice of Electroconvulsive Therapy by the American Psychiatric Association (1).

41.6. Number of Treatments

Typically patients are given 6–12 treatments. Some patients improve dramatically only after receiving 2–3 treatments while others do not even begin to improve until the 10th treatment. Although it is commonly believed that 90% of patients who receive ECT improve, in modern day practice the rate of improvement is much lower. In one study, if the Hamilton Depression

Rating Scale is used as a guide and if 50% or less is defined as treatment failure, the overall failure rate reached 58% (35). In the treatment non-responsive cases it is not uncommon to see that the total number of treatments reach 15–20.

Known evidence, thus far, indicates that there is no permanent brain damage associated with extended ECT (36, 37).

41.7. Adverse Reactions

About 50% of the patients report headache, nausea and muscle pain. The cause of post-ECT headache is not well known. It could be due to temporalis muscle spasm, acute increase in blood pressure (systolic pressure often reaches 200 or over) or other reasons. In most cases over-the-counter analgesics are enough; however, there are a good number of patients who complain of severe headache and for these patients a narcotic such as Tylenol #3 with Codeine, Percocet (oxycodone with acetaminophen: 2.5/325; 5/325; 7.5/500; 10/650 mg/mg), Vicodin (hydrocodone with acetaminophen: 5/500; 7.5/750; 10/660 mg/mg), Stadol (butorphanol) nasal spray or one of the other narcotics needs to be prescribed. Because most of these narcotics contain acetaminophen, each patient should be advised to avoid additional acetaminophen use. In case further analgesics are needed non-acetaminophen analgesics should be recommended.

Muscle aches are usually taken care of if the patient takes a headache medication. Although some believe that muscle aches come from the seizure, more commonly it is due to fine muscle fiber fasciculations following the use of succinylcholine. Pain coming from intense seizure, however, cannot and should not be ruled out.

Nausea is another common post-ECT side effect. A 5-HT_3 receptor antagonist such as ondansetron 4 mg I.V. (or 8 mg I.V.) is used quite often to counteract nausea. For those patients who still complain of nausea, an oral dopamine receptor antagonist is often used. Nausea may be associated with anesthesia, headache or vagus nerve stimulation (through the stimulation of area postrema within the nucleus tractus solitarius). Nausea and headache are often resolved during the later phase of ECT.

Some patients develop severe agitation during the recovery phase. I.V. Versed (midazolam) 2–4 mg is enough in some cases but in others a stronger measure is needed. Haldol (haloperidol) 5–10 mg I.V. or Zyprexa (olanzapine) 10 mg I.M. is often needed. Zydis (olanzapine sublingual preparation) 10 mg prior to ECT seems to prevent the agitation more effectively than some other measures.

Assessment of level of functioning, sensorium and memory should be performed at least once a week. The examination should not be done during the acute post-ictal phase because during this period patients often show disturbed sensorium and poor memory. Examination is usually conducted one day or more later using the "Mini Mental State" (38).

One exception is that with the advent of right unilateral ultra-brief pulse width ECT the post-ECT confusion period is significantly shortened. In the majority of the cases confusion resolves within one hour in contrast to several hours following traditional bilateral ECT.

41.8. Poor Treatment Response to ECT

ECT has been touted to be the most effective means of treating depression and this fact still stands; however, the rate of treatment response seems to be decreasing as mentioned previously and studies cited previously seem to support this fact..

Documented evidence suggests that concurrent use of antidepressants may augment ECT effects and a good number of patients are on one or more antidepressants while undergoing ECT. ECT specialists often switch to bilateral from unilateral mode and/or extend the number of ECT to 15–20 in the absence of response. Seizure dampening medications are double checked to ensure that patients are not on them. In reality, most patients have been screened for these possible confounding variables and are genuine poor ECT responders.

In extreme cases Vagus Nerve Stimulator, Deep Brain Stimulator (23) alone or in combination with ECT need to be considered. In the case of Vagus Nerve Stimulator implantation, for treatment of refractory depression (39), a coil shaped terminal is wrapped around left vagus nerve at the neck level and the connecting wire to the battery generator is guided subcutaneously over the clavicle. The battery generator itself is buried subcutaneously into the chest wall. The procedure is usually performed by a neurosurgeon or otolaryngologist. In the case of deep brain stimulator, a burr hole is created in the skull and the thin probe (wire with stimulator tip) is placed, under the physiologic guidance, in the proper place in the brain. The battery generator is buried subcutaneously into the chest. This procedure is performed by a trained neurosurgeon. For treatment of refractory depression, chronic stimulation of white matter tracts adjacent to the subgenual cingulate gyrus was associated with a striking and sustained remission of depression in four of six patients (40).

41.9. Post ECT Pharmacological Management

Treatments of unipolar or bipolar depression, be it through ECT or drugs, are temporary. If left alone most patients suffer relapse within 6 months to a year. In contrast to some who teach that depression is an episodic illness that needs to be managed for 6 months and then terminate treatment, most depressed patients who come to psychiatrists have chronic and recurrent depression and require multi-year management, if not life-time.

Thus, most psychiatrists continue to provide antidepressants and/or an augmenting agent after successful ECT. In spite of these measures, relapse rates, among psychotic or pre-ECT drug refractory depression cases remain high (41).

41.10. Continuation of ECT After Index Treatment

Continuation of ECT seems to bring out equal or better treatment outcome in comparison to pharmacotherapy (17, 42).

41.11. Maintenance of ECT

Maintenance of ECT is defined when ECT is extended beyond 6 months from the index treatment. Recent trends indicate that more patients are seeking maintenance ECT. Maintenance ECT has been successfully monitored for multi-year periods (clinical observation only), that is, 10 years or more; however, there is no research data in this area. In this case, the most common treatment mode is to give ECT every other week or in the range of 1–4 week intervals depending on each individual's clinical needs. This method is reserved for those who suffer recurrent depression and fail to respond to pharmacological or cognitive behavior therapy.

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Profiles in History of Neuroscience and Psychiatry

Timothy D. Folsom, M.S., Amelia Merz, M.D., Jon E. Grant, M.D., J.D., M.P.H., Neelufaar Fatemi, B.S., S. Ali Fatemi, M.D., and S. Hossein Fatemi, M.D., Ph.D., FACPsych

Abstract From the work of physicians, anatomists, and philosophers from the Medieval and Renaissance eras to the vast expansion of knowledge on brain anatomy and functioning during the 19th and early 20th century to the development of more refined treatments (particularly pharmacologic treatments), diagnostic criteria, and imaging techniques of the past 70 years, the history of psychiatry and neuroscience is a fascinating subject. This chapter profiles 82 historical and contemporary psychiatrists, neuroscientists, and scientists who have made substantial contributions to the diagnosis and treatment of psychiatric disorders.

Keywords Psychiatry · Neuroscience · Anatomy · Pharmacology · Brain · Schizophrenia · Genetics · Treatment · Behavior · Diagnosis · History

T.D. Folsom, M.S.
Junior Scientist, Department of Psychiatry, University of Minnesota School of Medicine, Minneapolis, MN, USA
e-mail: folso013@umn.edu

A. Merz, M.D.
Psychiatrist, Edward Hines Jr. Veterans Affairs Hospital, Hines, IL, USA

J.E. Grant, M.D., J.D., M.P.H.
Professor, Department of Psychiatry and Behavioral Neuroscience, University of Chicago Pritzker School of Medicine, Chicago, IL, USA
e-mail: jongrant@uchicago.edu

N. Fatemi, B.S.
University of Minnesota, Minneapolis, MN USA
e-mail: N.fatemi92@gmail.com

S.A. Fatemi, M.D.
Attending Cardiologist, Farabi Hospital, Tehran, Iran
e-mail: fatemi215@yahoo.com

S.H. Fatemi, M.D., Ph.D., FACPsych (✉)
Associate Chair for Neuroscience and Translational Research, Bernstein Endowed Chair in Adult Psychiatry, Professor, Departments of Psychiatry and Neuroscience, University of Minnesota School of Medicine, Minneapolis, MN, USA
e-mail: fatem002@umn.edu

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George Kevork Aghajanian

George Aghajanian is an American psychiatrist who has been instrumental in the study of neuropharmacology. Aghajanian was born in Beirut, Lebanon in 1932 and received his medical degree from Yale University in 1958. He did his residency in psychiatry. He joined the department of pharmacology at Yale University in 1970 and is currently an Emeritus Professor and Senior Research Scientist at the Yale University Department of Psychiatry.

Aghajanian is widely known for his work on the mode of action of lysergic acid diethylamide (LSD) through its binding to serotonin 2A receptors. He has also demonstrated that atypical antipsychotic drugs such as clozapine and risperidone inhibit the excitation of serotonin 2 receptors within clinically relevant doses. He proposed that this antagonism of serotonergic action may be a key part of their mode of action. More recently, Aghajanian and colleagues at Yale have focused on the role of ketamine as a novel antidepressant. Unlike typical antidepressants which take weeks to work, low doses of ketamine are known to alleviate symptoms of depression within hours. Aghajanian and colleagues found that ketamine treatment provides a more robust effect on glutamate transmission and release of brain derived neurotrophic factor (BDNF). Similar to long-term potentiation (LTP), this process produced more synaptic connections. The action of BDNF is dependent on inhibition of glycogen synthase kinase 3 (GSK3). The synaptic connections produced by ketamine treatment are short lived (7–10 days); however, these studies point to a new method for treating depression through targeted inhibition of GSK3.

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Aloyius "Alois" Alzheimer

Alois Alzheimer was a German psychiatrist, born in 1864, who first described the neuropathology of "presenile dementia," which his colleague, Emil Kraepelin, would later rename "Alzheimer's disease." In 1901, while working at the Frankfurt Asylum, Alzheimer met a 51-year-old female patient who had strange behavior and a progressive loss of short-term memory. He followed the patient over the next 6 years and, upon her death, biopsied her brain using Nissl staining technique and identified amyloid plaques and neurofibrillary tangles. In 1907, he presented his finding in a work entitled "*Uber eine eigenartige Erkrankung der Hirnrinde*," a landmark paper which first linked brain pathology and the clinical symptoms of presenile dementia. Alzheimer's advances in our understanding of dementia led to the recognition that it was a disease, as opposed to a normal age-related occurrence.

Following the receipt of his medical degree from Wurzburg University in 1887, Alzheimer took a position at the Stadtisch Anstalt fur Irre und Epileptische (asylum for lunatics and epileptics) at Frankfurt am Main. It was there that he learned the method of silver staining histological sections from his colleague, neurologist Franz Nissl. Alzheimer then went to work in Kraepelin's Munich laboratory, where he studied the cerebral atherosclerosis, general paresis of the mentally ill, and the effects of alcoholism and acute syphilitic infection on the brain. Kraepelin's view that psychiatric illnesses had a biologic cause was highly influential on Alzheimer. Subsequent to his work, we now know that both presenile (familiar) and senile dementias have a similar pathology and a unified biochemical pathogenesis. After 100 years of research, genetic studies are now leading us to novel therapies that target the amyloid process and hold potential to ameliorate the lives of patients with Alzheimer's disease. He died in 1915.

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Jules Angst

Jules Angst is a Swiss psychiatrist who is one of the pioneers of pharmacotherapy, and is known for his use of longitudinal studies which have provided key insights into psychiatric disorders. Angst's work in pharmacotherapy includes introduction and testing of antidepressants, lithium and antipsychotics. He contributed to the development of an objective and standard methodology to test for the efficacy, safety, and side-effects of such agents. Jules Angst's longitudinal studies have yielded important results on the long-term course of schizophrenia, schizoaffective and mood disorders. The most famous of Angst's studies is the Zurich Study, which has produced comprehensive data on variables related to health, behavior, symptoms, personality, and overall functioning. Cross-sectional assessments have provided important information on suicidiality, mood and anxiety disorders, psychosomatic and neurasthenic syndromes, the incidence and course of the frequent disorders among adults as well as many other topics.

Jules Angst received his medical degree from the University of Zurich in 1952. In 1953, he began his career at the Burghölzli, ultimately becoming the head of the Head of the Burghölzli Research Department in 1969, a position he held until his retirement in 1994. Jules Angst has received numerous awards for his work including the Emil Kraepelin Gold Medal from the Max Planck Institute in 1992 and the Burghölzli Award in 2001.

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Gustav Aschaffenburg

Gustav Aschaffenburg was a German psychiatrist and a pioneer in forensic psychiatry and criminology. He was born in Zweibrücken and received his medical doctorate in 1890 from the University of Strasbourg. Aschaffenburg worked as an assistant to Emil Kraepelin in Heidelberg. At Heidelberg, he was chief physician of the Monitoring Department of the criminally insane at the prison. It was during this time that he first formulated his theories about criminal behavior. Aschaffenburg was later a professor of psychiatry at the University of Halle and the University of Cologne. In the 1930s, he was dismissed from his academic position by the Nazis. He immigrated to the USA working first at the Catholic University of America and later Johns Hopkins University where he taught as a professor of criminal psychology. In 1942, he was made an honorary member of the American Psychiatric Association. He died in 1944.

In 1903, with the encouragement of Kraepelin, Aschaffenburg produced one of the first scientific analyses of the origins of criminal behavior titled *Das Verbrechen und seine Bekampfung*, which was translated into English in 1913 as *Crime and its Repression*. Aschaffenburg stressed both heredity and social or environmental factors as elements underlying criminal behavior, rejecting the idea that criminals were born that way. He presented data on social factors such as urban vs. rural setting, economic conditions, alcohol abuse, nationality, and religion. In the section on individual causes of crime, Aschaffenburg again stressed the environment that produced criminals as well as intellectual deficits in criminals. In 1904, he founded the journal *Monatsschrift für Kriminalpsychologie und Strafrechsreform*, which was the leading criminology journal for decades.

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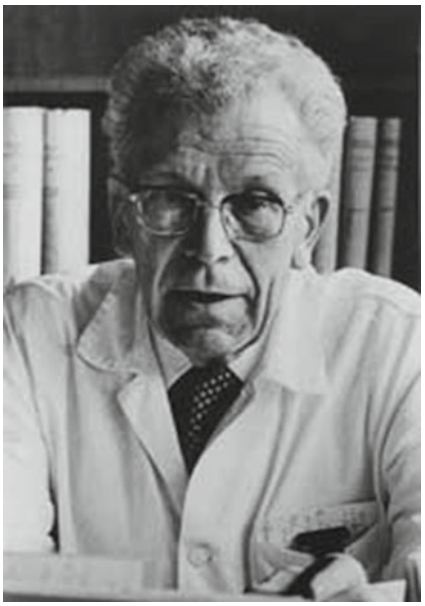
Hans Asperger



Hans Asperger was an Austrian psychiatrist who in 1944 described a set of autistic symptoms that are now known as Asperger's syndrome. Asperger was born in 1906 in Vienna, Austria. As a child, Asperger displayed features of the condition that was later named for him such as difficulty in social interactions. He received his medical degree in 1931 from the University of Vienna. Asperger worked at the University of Vienna, Department of Pediatrics from 1944 until 1977. He also served as Professor of Pediatrics at the University of Innsbruck and the Director of Children's Hospital at the University of Vienna.

In 1944, Asperger first described "autistic psychopathy" as including lack of empathy, impaired ability to form friendships, intense interest in a specific topic, clumsy movements, and impaired conversational ability (i.e., subjects engaged in one-sided conversations). These symptoms were initially identified in four boys and later in a number of children treated at the Children's Hospital. Asperger referred to these patients as "little professors" due to their ability to talk at great length and detail on their particular fields of interest. It was not until after Asperger's death in 1980 that his findings, now referred to Asperger's syndrome, were translated into English and found more widespread acceptance including inclusion in the ICD-10 in 1993 and the DSM-IV in 1994. Today, Asperger's syndrome is generally thought of as part of autism spectrum disorder.

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Avicenna

Avicenna (Abu Ali Sina) was a Persian physician, scientist, and philosopher whose 14-volume *The Cannon of Medicine* served as the primary medical text at European universities for nearly 500 years. The *Cannon* detailed and classified diseases including their presumed causes. It includes a description of symptoms and complications of diabetes. Additionally, hygiene, pathology, medicines, and bodily functions are described. Avicenna was the first to correctly describe the anatomy of the human eye and afflictions of the human eye such as cataracts, emphasized contagion of tuberculosis, and described facial paralysis. Avicenna also had an interest in psychology and wrote extensively on the effect of emotions on physical conditions and referred to topics related to insanity, melancholia, agitation, hysteria, alcoholic intoxication, and mental confusion.

Avicenna was born in 980 in Afshana near Bokhara. He received his medical training at 16, attaining full status as a physician at age 18. He worked throughout his career, moving from place to place, for various governmental officials. In addition to the Cannon, Avicenna published numerous works on medicine, philosophy, and logic. He died in 1037 in Hamadan, Iran.

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Julius Axelrod

Julius Axelrod was born in 1912 in New York City. After receiving his B.S. from College of the City of New York in 1933, Axelrod worked as a Laboratory Assistant at the Department of Bacteriology of New York University Medical School. He received his M.A. from New York University in 1941 while he was a chemist at the Laboratory of Industrial Hygiene. In 1950, he began his career at NIH as an associate chemist in the Section on Chemical Pharmacology, National Heart Institute. He became Senior Chemist in 1953, and was appointed Chief of the Section on Pharmacology, Laboratory of Clinical Science, National Institute of Mental Health, Health Services and Mental Health Administration, Department of Health, Education and Welfare in 1955. Also in 1955, Axelrod received his Ph.D. from George Washington University. He continued to work at the National Institute of Mental Health until his death in 2004.

In 1970, Julius Axelrod received the Nobel Prize for his work on the release, reuptake and storage of the neurotransmitters epinephrine and norepinephrine, also known as adrenaline and noradrenaline. Working on monoamine oxidase (MAO) inhibitors in 1957, Axelrod showed that catecholamine neurotransmitters do not merely stop working after they are released into the synapse. Instead, neurotransmitters are recaptured ("reuptake") by the presynaptic nerve ending, and recycled for later transmissions. He theorized that epinephrine is held in tissues in an inactive form and is liberated by the nervous system when needed. This research laid the groundwork for later development of selective serotonin reuptake inhibitors (SSRIs).

Some of Axelrod's later research focused on the pineal gland. He and his colleagues showed that the hormone melatonin is generated from tryptophan, as is the neurotransmitter serotonin. The rates of synthesis and release follow the body's circadian rhythm driven by the suprachiasmatic nucleus within the hypothalamus. Axelrod and colleagues went on to show that melatonin had wide-ranging effects throughout the central nervous system, allowing the pineal gland to function as a biological clock.

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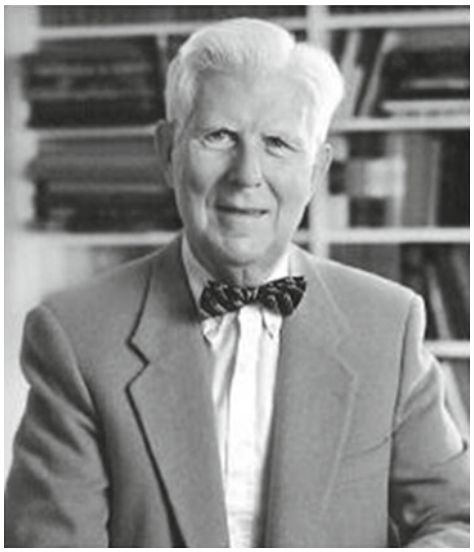
Aaron T. Beck



Aaron Temkin Beck is an American psychiatrist and a professor emeritus at the University of Pennsylvania and is known as the father of cognitive behavioral therapy (CBT). His work in psychotherapy led him to believe that depression was due to unrealistic, negative views directed at the self, the world, and the future. Through his research in psychotherapy, psychopathology, suicide, and psychometrics, he developed cognitive behavior therapy and subsequently, the Beck Depression Inventory (BDI), one of most widely used tools for assessing the severity of depression.

Beck was born in 1921 and raised in Providence, Rhode Island and received his undergraduate degree from Brown University, graduating magna cum laude in 1942. He studied medicine at Yale University and followed his graduation in 1946 with a residency in neurology at the Cushing Veterans Hospital in Framingham, MA. A required rotation in psychiatry intrigued him and he decided to explore psychotherapy. He then spent 2 years at the Austin Riggs Center in Stockbridge studying long-term psychotherapy and in 1954, accepted a position in the Department of Psychiatry at the University of Pennsylvania where he is currently an emeritus professor. His work on prevention of suicide with short-term CBT has been funded by the M.E.R.I.T. Award from the National Institute of Mental health and from the Centers for Disease Control. His most recent work focuses on reducing suicide attempts among chronic attempters and in patients with borderline personality disorder.

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Lauretta Bender

Lauretta Bender was an American psychiatrist who was instrumental in the study of childhood schizophrenia. Bender was born in Butte, Montana and received her medical degree from the University of Iowa in 1926. Following psychiatric training at Boston Psychopathic Hospital, and a research associate position at Johns Hopkins University, Bender worked at the psychiatric department at Bellevue Hospital in New York City from 1934–1956. It was at Bellevue Hospital that Bender began studying schizophrenia in children, believing that childhood schizophrenia had an organic origin. At Bellevue, she performed controversial experiments examining the effect of electroconvulsive therapy (ECT) on children. She is best known for developing the Bender Visual Motor Gestalt Test in 1938 which is a measure of perceptual motor skills, perceptual motor development, and neurological state. Bender was later a professor at Columbia University and, subsequently, at the University of Maryland. She died in 1987.

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Hans Berger

Hans Berger was a German neurologist and psychiatrist who invented electroencephalography (EEG). Berger was born in 1873 in Coborg. He received his medical degree from Friedrich Schiller University of Jena in 1897. It was at Jena in 1924, that Berger successfully recorded the first human EEG by inserting silver wires under the scalp at the front and back of the subject's head which were connected to a galvanometer. When he published his results in 1929 they were greeted with skepticism by the German medical establishment. However, his results were confirmed in 1934 by British scientists Edgar Douglas Adrian and Bryan H. C. Matthews, and eventually gained widespread recognition. Through his experiments, Berger was able to identify different brain waves that were present in the brains of normal and abnormal subjects. He described alpha waves (also known as Berger waves) which are present during a relaxed state with eyes closed, and diminish or disappear when the subject's eyes are open. Additionally, Berger studied differences in EEG activity in subjects who were diagnosed with epilepsy. Today EEG is used to help diagnose epilepsy, sleep disorders, coma, delirium, and brain death. Berger continued to work at Jena until 1938 when he retired. After a long bout of clinical depression he committed suicide in 1941.

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Otto Binswanger

Otto Binswanger was a Swiss psychiatrist and neuroanatomist. He was born in 1852 and was part of a family of influential psychiatrists including his father Ludwig Binswanger (1820–1880) who founded the Kreuzlingen mental asylum, his brother Robert Binswanger (1850–1910) who later assumed leadership of the Kreuzlingen asylum, and his nephew Ludwig Binswanger (Robert's son; 1881–1966) who introduced the concept of "daseinsanalyse," an existentialist method of psychoanalysis. Binswanger studied medicine in Zurich, Heidelberg, and Strasbourg and worked at psychiatric clinic at the University of Göttingen, the pathological institute in Breslau, and the psychiatric and neurological clinic at Charité Hospital in Berlin. In 1882, he was appointed the director of the mental asylum at Jena as well as a professor of psychiatry, positions he held until his retirement in 1919. Binswanger had wide-ranging interests in psychiatry including epilepsy, hysteria, and neurasthenia. His 1899 textbook *Epilepsy*, was for many years, a standard text for the study of this disorder. In 1894, Binswanger described a condition of subcortical vascular dementia which he termed "encephalitis subcorticalis chronica progressive" caused by damage to white matter of the brain. This disorder is characterized by white matter atrophy, loss of memory, intellectual impairment and mood changes. Alois Alzheimer confirmed Binswanger's findings through pathological evidence and referred to the disorder as Binswanger's disease. While at Jena, Binswanger worked with a number of important psychiatrists including Hans Berger (1873–1941), Korbinian Brodmann (1868–1918), Oskar Vogt (1870–1959), and Theodor Zlehen (1862–1950). Following his retirement, Binswanger returned to Kreuzlingen where he died in 1929.

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Paul Eugen Bleuler

Paul Eugen Bleuler was a Swiss psychiatrist most notable for his contributions to the understanding of mental illness and the naming of schizophrenia. Bleuler was born in 1857 in Zollikon, a small town near Zürich in Switzerland. He studied medicine in Zürich, and later studied in Paris, London, and Munich after which he returned to Zürich to take a post as an intern at the Burghölzli, a university hospital. In 1886, Bleuler became the director of a psychiatric clinic at Rheinau, later returning to Burghölzli as director in 1898. During his time as director he employed Carl Jung as an intern. He died in 1940.

Bleuler is particularly notable for naming schizophrenia, a disorder which was previously known as dementia praecox. Bleuler realized the condition was neither a dementia, nor did it always occur in young people (praecox meaning early) and so gave the condition the purportedly less stigmatizing but still controversial name from the Greek for split (schizo) and mind (phrene). Bleuler introduced the term "ambivalence", in 1911; introduced the term "autism" in a 1912 edition of the American Journal of Insanity, and described schizoid personality.

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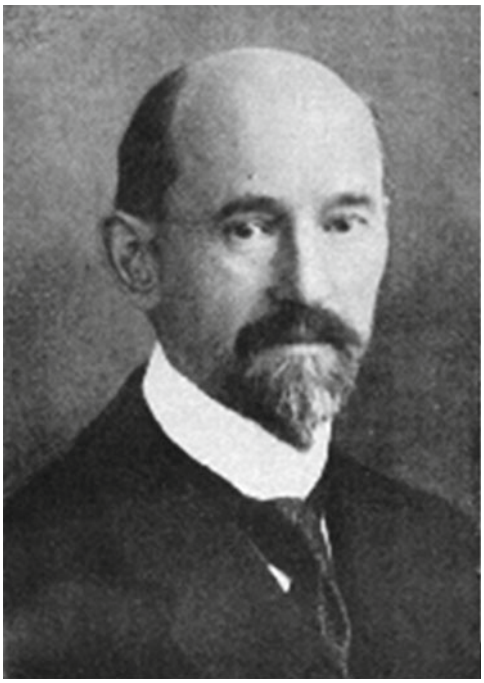
Korbinian Brodmann



Korbinian Brodmann was a German neuroanatomist best known for his division of the cerebral cortex into 52 regions based on their characteristics. Brodmann was born in 1868 in Liggersdorf, Germany and received his doctor of medicine degree from the University of Leipzig in 1898. He worked at the psychiatric clinic at the University of Jena with Ludwig Binswanger and later at the Municipal Mental Asylum in Frankfurt where he met Alois Alzheimer. Alzheimer encouraged Brodmann to pursue neuroanatomical research. In 1909, Brodmann published his research on the cerebral cortex, *Comparative Localization Studies in the Brain Cortex*, *its Fundamentals Represented on the Basis of its Cellular Architecture*. Brodmann characterized 52 regions of the cortex and organized them into 11 histological areas. In his mapping of the brain Brodmann used gross anatomy as well as the cytoarchitectural organization of neurons using Nissl staining as guidelines for defining each region. He proposed that each region would likely have a unique function. Later research proved this correct for selected regions including Brodmann Areas (BA) 41 and 42 in the temporal lobe being associated with hearing; BA17, BA18, and BA19 in the occipital lobe associated with vision; and BA44 and BA45 (Broca's area) involved in speech. Following the publication of his research, Brodmann held positions at the University of Tübingen, and finally the University of Munich. He died in 1918. Today, Brodmann areas remain the most cited cytoarchitectural organizations of the cerebral cortex.

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John Frederick Joseph Cade

John Cade was an Australian psychiatrist who discovered the efficacy of lithium for the treatment of mania. Cade was born in Mutora, Australia in 1912 and received his medical degree from the University of Melbourne in 1933. Following his graduation, Cade worked at St. Vincent's Hospital and Royal Children's Hospital before serving in World War II as a medic. He was captured by Japanese troops after the fall of Singapore in 1942 and remained a prisoner of war until 1945. Following his release, Cade worked as a psychiatrist at the Repatriation Mental Hospital, Bundoora. In 1952, he became the Superintendent and Dean of the Royal Park Psychiatric Hospital where he served until his retirement in 1977. He died in 1980.

Early during his time at the Repatriation Mental Hospital, Bundoora, Cade suspected that the manic symptoms he observed in his patients were the result of a metabolic disorder resulting from an excess toxin which was excreted in their urine. Cade tested his hypothesis by injecting guinea pigs with the urine of mentally ill patients, which showed toxic properties in the guinea pigs. When the urine was injected with lithium carbonate (which was included to increase water solubility of uric acid), the toxicity was reduced and the animals exhibited lethargy. After testing lithium salts on himself, to test its safety, he then treated ten patients with chronic or recurrent mania. He found that treatment with lithium had a calming effect, similar to what he had observed in the guinea pigs. This discovery revolutionized the treatment of bipolar disorder, which had previously been treated with electroconvulsive therapy and hospitalization.

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Santiago Ramón y Cajal

Santiago Ramón y Cajal was a Spanish anatomist known for his studies of the fine structure of the central nervous system. Using a histological staining technique pioneered by Camillo Golgi, Ramón y Cajal's work led him to postulate that the nervous system is made up of billions of individual cells (rather than a web of interconnected cells like the circulatory system; Golgi's hypothesis) and that these cells are polarized. Ramón y Cajal proposed that these cells communicate with one another at specialized junctions (later termed synapses by Sir Charles Scott Sherrington in 1897). Ramón y Cajal was also the first to describe the axonal growth cone and proposed that it was responsible for axonal outgrowth.

Ramón y Cajal was born in 1852 and received his licentiate in medicine at the University of Zaragoza in 1873. He later received his doctorate of medicine at Madrid and was appointed as a university professor at the University of Valencia. He later had professorships in Barcelona and Madrid and was appointed as the director of the National Institute of Hygiene in 1900. Ramón y Cajal also founded the *Laboratorio de Investigaciones Biológicas* in 1902 which was later renamed the *Instituto Cajal* or Cajal Institute upon his retirement in 1922. During his career Ramón y Cajal published over one hundred articles on his findings, primarily on the fine structure of the brain and spinal cord but also on muscles and various subjects in the fields of anatomy and pathology. He also published books, the most important being the *Manual de Histología normal y Técnica micrográfica* (Manual of Normal Histology and Micrographic Technique) published in 1889. Among his many distinctions and honors, Ramón y Cajal was made an honorary doctor of medicine at the Universities of Cambridge and Würzburg and shared the 1906 Nobel Prize in Physiology or Medicine with Camillo Golgi. He died in 1934.

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Arvid Carlsson

Arvid Carlsson is a Swedish physician and neuropharmacologist who discovered the role of the neurotransmitter dopamine in Parkinson's disease. He shared the 2000 Nobel Prize in Physiology and Medicine with his colleagues Eric Kandel and Paul Greengard. Carlsson's work established dopamine as a critical neurotransmitter, showing that high levels are found in areas of the brain that control walking and voluntary movements. He discovered that levodopa, a substance in the brain used to make dopamine, could be used in the treatment of Parkinson's disease. His work demonstrated that dopamine was an active neurotransmitter, not just a precursor to norepinephrine, as had been previously believed. Carlsson's research lead to our current understanding of the relationship between neurotransmitters and mental disorders such as schizophrenia and depression and ultimately lead to the development of medications such as Prozac (fluoxetine), one of the most widely used medications for the treatment of depression.

Carlson was born in 1923 in Sweden and received his medical degree from Lund University in 1951. After medical school, he decided to pursue a career in research and took a position at Lund University in the Department of Pharmacology. There he studied calcium metabolism and completed a doctoral thesis that related to the necessity of vitamin D in calcium absorption and regulation. He then took a position as a professor at the Goteborg University where he continued his research delineating how nerve cells communicate.

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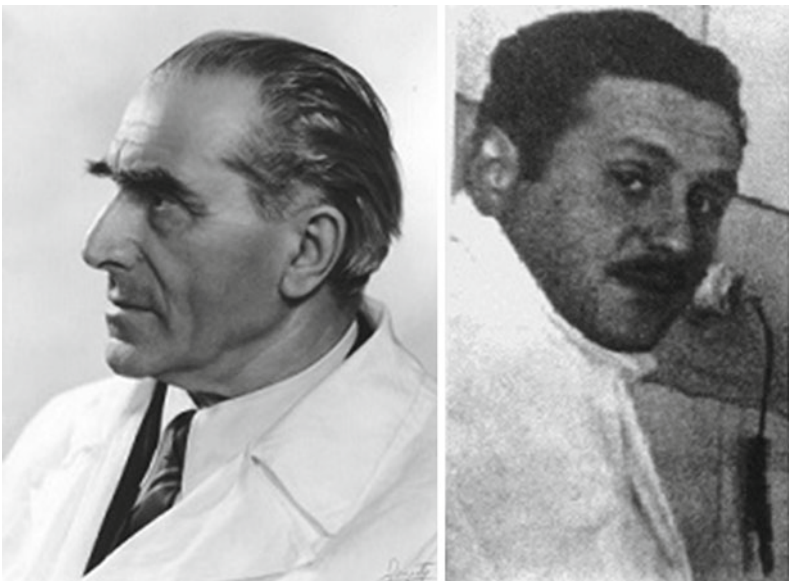
Ugo Cerletti and Lucio Bini



Ugo Cerletti was an Italian neurologist and psychiatrist and Lucio Bini was an Italian psychiatrist who together invented electroconvulsive therapy (ECT) as a treatment in psychiatry. Cerletti was born in Conegliano in 1877 and studied medicine in Rome and Turin. Bini was born in 1908. In 1938, while at the University of Rome La Sapeinza, Cerletti, Bini, and colleagues (Ferdinando Accornero and Lamberto Longhi) developed ECT with the idea of treating subjects with schizophrenia. At the time, some thought that induction of seizures would prevent schizophrenia. Prior to ECT, metrazol and insulin had been used to induce seizures. It was Cerletti who proposed replacing these pharmacologic methods with the use of electrical stimuli. The team of researchers successfully tested ECT on a subject with schizophrenia who presented with delusions and hallucinations. The patient returned to a normal state of mind, demonstrating clinical efficacy for ECT. As a clinician, Bini established proper guidelines for the use of ECT. Moreover, Bini elaborated on the technique by including bitemporal placement of electrodes, which greatly reduced the danger of previous procedures. Following the first successful test, ECT was used to treat schizophrenia, bipolar disorder, and major depression. Cerletti died in Rome in 1963. Bini died in Rome in 1964.

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Paul Charpentier

Paul Charpentier was a French Chemist who synthesized chlorpromazine (CPZ) in 1951 at the laboratories of Rhône-Poulenc, a pharmaceutical company. Charpentier was interested in developing new antihistamines and produced a drug called promethazine, an antihistamine that displayed strong sedative effects. Using promethazine as a nucleus, Charpentier synthesized additional compounds, one of which was CPZ. CPZ is a dopamine antagonist and the first antipsychotic agent. CPZ was first marketed in France in 1952 and then in the USA in 1954 as Thorazine. The first psychiatric patient to receive CPZ was an agitated, psychotic subject who was given a 50 mg intravenous injection. There was an immediate calming effect which lasted several hours. Following repeated injections of CPZ along with treatment with barbiturates and ECT, the patient's symptoms were resolved. The use of CPZ revolutionized the treatment of schizophrenia and led to the development of additional typical and atypical antipsychotic drugs based on dopamine antagonism.

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Erminio Costa

Erminio Costa was born in Cagliari, Italy in 1924. His long career in scientific research began in 1947, when he earned his M.D. at the University of Cagliari, Italy, and was appointed Associate Professor (1948) and then Professor of Pharmacology (1954) at that University. In 1961, Costa became Deputy Chief of the National Heart Institute's Laboratory of Chemical Pharmacology at the National Institutes of Health (NIH). In 1968, Costa founded and for 17 years directed the prestigious Laboratory of Preclinical Pharmacology (LPP) of the National Institute of Mental Health. In 1985, Costa founded and became Director of the Fidia-Georgetown Institute for the Neurosciences (FGIN) and Professor in the Departments of Anatomy and Cell Biology and Pharmacology at Georgetown University, Washington, D.C. until 1994. In 1996, Erminio Costa was appointed the Scientific Director of the Psychiatric Institute and Professor of Biochemistry in Psychiatry, University of Illinois at Chicago, Chicago, Illinois. He died in 2009.

Erminio Costa's professional research activity spanned over 60 years and he spent several decades studying the pathophysiology and treatment of schizophrenia starting with; (1) pioneering studies on the identification and measurement of serotonin in the human brain of normal and psychiatric patients; (2) the discovery that anxiolytic benzodiazepines act by allosterically positively modulating GABA actions at specific GABAA recognition sites; and (3) extending his interest on GABAergic dysfunction as a fundamental event in schizophrenia pathophysiology, as reflected by deficits in Reelin and GAD 67 proteins in brains of subjects with schizophrenia, and psychotic bipolar disorder.

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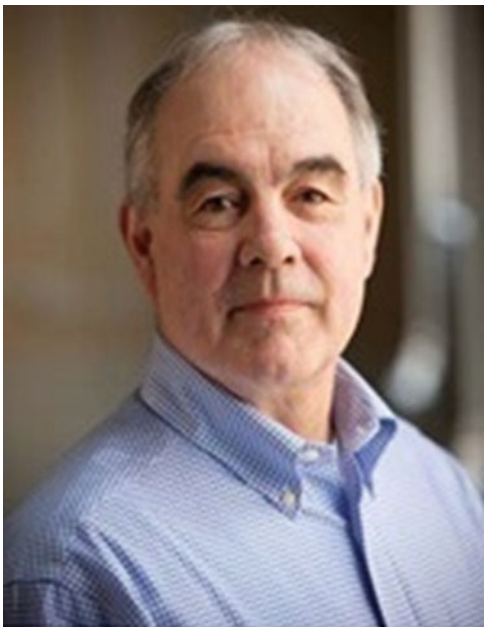
Joseph T. Coyle



Joseph T. Coyle is an American psychiatrist who has made key findings in the study of neurodevelopmental and neurodegenerative diseases that have opened up new avenues of therapeutic intervention. He received his medical degree from Johns Hopkins University in 1969 and following an internship in pediatrics, worked as a Research Fellow under the direction of Julius Axelrod at the National Institutes of Health. Coyle completed his residency in psychiatry at Johns Hopkins University in 1976 and served as the Director of the Division of Child and Adolescent Psychiatry. Coyle served as Chair for the Department of Psychiatry at Harvard Medical School from 1991–2001. He is a past President of the American College of Neuropsychopharmacology and the Society for Neuroscience. Coyle is currently the Eben S. Draper Chair of Psychiatry and Neuroscience at Harvard Medical School and Chief of the Division of Basic Neurosciences and Chief Scientific Officer of McLean Hospital. He has received numerous awards for his research including the A.E. Bennett Award from the Society for Biological Psychiatry, the Lieber Prize for Research on Schizophrenia from NARSAD, and the Julius Axelrod Award for Neuropharmacologic Research from the Society for Neuroscience.

Coyle's research has focused on developmental neurobiology, mechanisms of neuronal vulnerability as well as psychopharmacology. His research has contributed greatly to the understanding of pathological changes associated with psychiatric and neurodegenerative disorders. Coyle and colleagues identified that a loss of cholinergic neurons in the basal forebrain was associated with Alzheimer's disease. This finding has opened the way for targeted treatment for this disorder. More recently Coyle has focused on glutamate and schizophrenia, specifically hypofunction of NMDA glutamate receptors and the use of drugs such as D-cycloserine, a partial NMDA receptor agonist, for the treatment of negative symptoms of schizophrenia.

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Jacqueline N. Crawley

Jacqueline Crawley is an American neuroscientist who has used mouse models to test hypotheses regarding the genetic basis of autism and to identify new treatments for this disorder. She received her Ph.D. from the University of Maryland, College Park in 1976. From 1983 through 2012, she was the chief of the Laboratory at the National Institute of Mental Health (NIMH) Intramural Research Program. Since 2012, she has been the Robert E. Chason Endowed Chair in Translational Research at the University of California, Davis MIND Institute. She has published over 275 peer-reviewed research articles and her research has earned her numerous awards including the Special Achievement Award from NIMH, the Distinguished Investigator Award from the International Behavioural and Neural Genetics Society, and the Marjorie A. Meyers Lifetime Achievement Award from the International Behavioral Neuroscience Society.

Crawley has performed extensive experiments employing behavioral tests relevant to autism in transgenic and knockout mouse models studying autism candidate genes such as SH3 and multiple ankyrin repeat domains 1 (Shank1), Shank3, tuberous sclerosis 1 (Tsc1), and fragile X mental retardation 1 (Fmr1). To evaluate core features of autism, Crawley has developed widely employed tests including a light–dark exploration test to measure anxiety and the three-chambered compartment test to evaluate social behavior. Crawley and colleagues have also modeled impaired social communication through olfactory communication and ultrasonic vocalizations as well as repetitive behaviors through marble burying tasks. From these experiments, Crawley has paved the way to test drugs for efficacy in the treatment of autism including recent work on metabotropic glutamate receptor 5 (mGluR5) antagonists.

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Karl Deisseroth

Karl Deisseroth is an American psychiatrist who has created and developed the technologies of CLARITY and optogenetics. He received his Ph.D. in neuroscience in 1998 and M.D. in 2000 from Stanford University. Deisseroth completed his residency in psychiatry at Stanford University where he is currently the D.H. Chen Professor of Bioengineering and Psychiatry. Additionally, he is a Foreign Adjunct Professor at the Karolinska Institute and an Investigator at the Howard Hughes Medical Institute. He has earned widespread recognition for his work on optogenetics and CLARITY including the Richard Lounsbery Prize from the National Academy of Sciences, the Top Ten Technologies Award from MIT Technology Review, and most recently, the Keio Medical Science Prize.

Beginning in 2004, Deisseroth began a series of experiments with neurons which have been genetically engineered to be sensitive to light. This technology was termed optogenetics and has been used to not only monitor, but to control the activity in neurons in vivo. Deisseroth and his group were able to control the behavior of freely moving animals as well as compel unrestrained, sleeping animals to wake up by targeting certain neurons in the hypothalamus. Optogenetics has been applied to help explain how to optimally place electrodes to stimulate the brain in Parkinson's disease. A second important technology developed by Deisseroth is Clear, Lipid-exchanged Acrylamide-hybridized Rigid Imaging/immunostaining compatible Tissue hYdrogel (CLARITY) which makes brain tissue transparent by dissolving the brain's lipid tissue while keeping the proteins and nucleic acids intact. The result allows for an unobstructed view of brain structures and circuitry. A recent application of CLARITY has been the production of brain-wide maps of neurons that produce dopamine.

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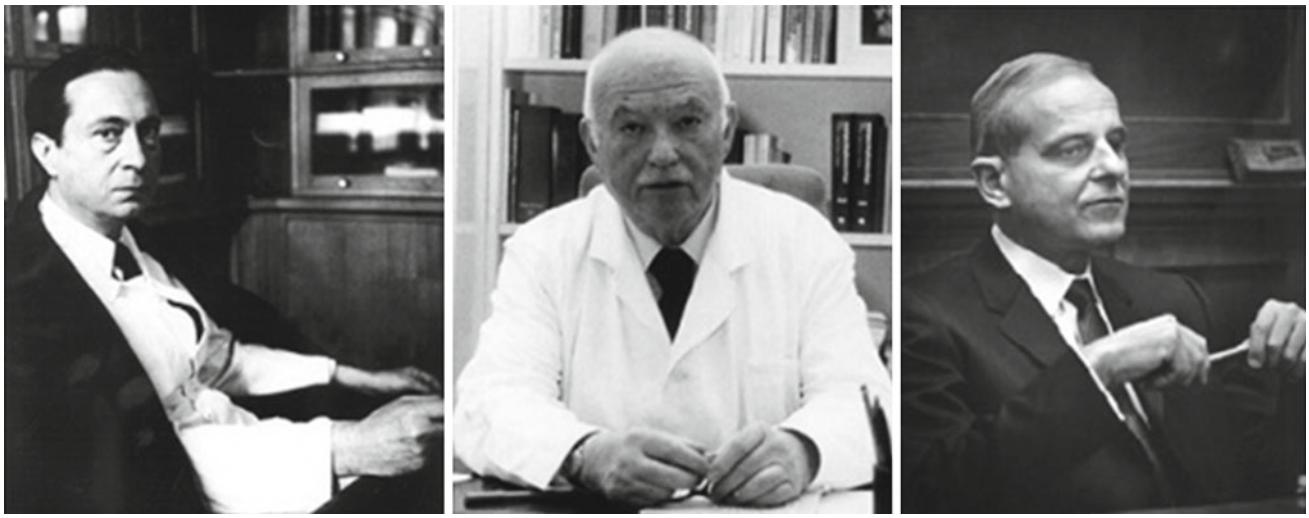
Jean Delay, Pierre Deniker, and Heinz Lehmann



Jean Delay (1907–1987) and Pierre Deniker (1917–1998) were French psychiatrists involved in the first trials of chlorpromazine (CPZ) at the Sainte-Anne hospital in Paris. Delay received his medical degree along with degrees in literature and philosophy from the Sorbonne, while Deniker received his degree from the Faculty of Medicine (Paris). They received samples of CPZ from Rhône-Poulenc and administered the drug in successive doses, reporting that daily doses of 75 mg were sufficient to control psychosis in psychiatric patients without resulting in excessive sedation. Heinz Lehmann (1911–1999) was a German born, Canadian psychiatrist who tested CPZ in patients with schizophrenia at Verdun Protestant Hospital in Montreal. He was the first to hypothesize that CPZ inhibits affective drive and his published results paved the way for CPZ use in North America. Deniker and Lehmann, along with Henri-Marie Laborit, received the Lasker Award for their roles in developing the use of CPZ for the treatment of psychiatric disorders.

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Hermann Ebbinghaus

Hermann Ebbinghaus was a German Psychiatrist who was a pioneer in the study of memory. Ebbinghaus was born in Barmen in 1850 and received his doctorate from the University of Bonn in 1874. Subsequently, he taught in England and France before returning to studies at the University of Berlin where he began his experiments with memory in 1879. In 1885, he published the results of his studies in *Memory*: *A Contribution to Experimental Psychology*, which is considered a monumental work. He continued as a Professor at the University of Berlin until 1894 when he joined the University of Breslau. In 1902, he published *Fundamentals of Psychology*, which was an immediate success. He spent the last few years of his life in Halle where he published *Outline of Psychology* in 1908 which was also highly influential. Ebbinghaus died in 1909.

Ebbinghaus was interested in showing that higher mental processes such as memory could be studied experimentally, which was an unpopular idea at the time. In *Memory*: *A Contribution to Experimental Psychology*, he detailed experiments that described processes of learning and forgetting. He described the forgetting curve or the time it takes to forget learned information. There was an exponential loss with the steepest decline within the first 20 minutes, and remained significant within the first hour with a gradual leveling off by the end of the first day. Ebbinghaus was the first to use the term "learning curve" to describe how quickly information can be learned. The learning curve was also exponential with the sharpest increase occurring after the first try and then leveling off with less new information retained after subsequent repetitions. Ebbinghaus is also credited with pioneering sentence completion exercises, which were later incorporated into the Binet–Simon Intelligence Scale. Finally, he discovered an optical illusion, now known as the Ebbinhaus illusion which tests relative size perception. It is currently used in cognitive psychological research to investigate perception pathways in the brain.

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Constantin von Economo

Constantine von Economo was an Austrian psychiatrist best known for characterizing encephalitis lethargica and for his brain atlas *Cytoarchitectonics of the Adult Human Cerebral Cortex*. He was born in 1876 in Brăila, Romania. Originally interested in engineering, Economo switched his studies to medicine, receiving his degree in 1901 from the University of Vienna. Following his residency, Economo traveled throughout Europe working in laboratories of neurology, histology and psychiatry; and undertaking microscopic analysis of the nervous system. During this period, he worked with Emil Kraepelin and Alois Alzheimer in Munich. He became a lecturer at the University of Vienna and, following his military service in World War I, was appointed a Professor of Psychiatry and Neurology in 1921. He conducted research at the Clinic for Psychiatry and Nervous Diseases in Vienna until his death in 1931.

Economo characterized the pathology, histology, and symptoms of encephalitis lethargica, an acute inflammation of gray matter that led to lesions in the substantia nigra. Beginning in 1912, Economo began his detailed study to divide the cortex by its cytoarchitecture. Published in 1925 as an 800 page, two-volume set, *Cytoarchitectonics of the Adult Human Cerebral Cortex*, divided the cortex into seven lobes: lobus frontalis, lobus limbicus superior, lobus insulae, lobus parietalis, lobus occipitalis, lobus temporalis, and lobus limbicus inferior/lobus hippocampi. The main thesis of the atlas was that cytoarchitectonic differences in brain anatomy reflect functional differences, which created the basis of future brain research.

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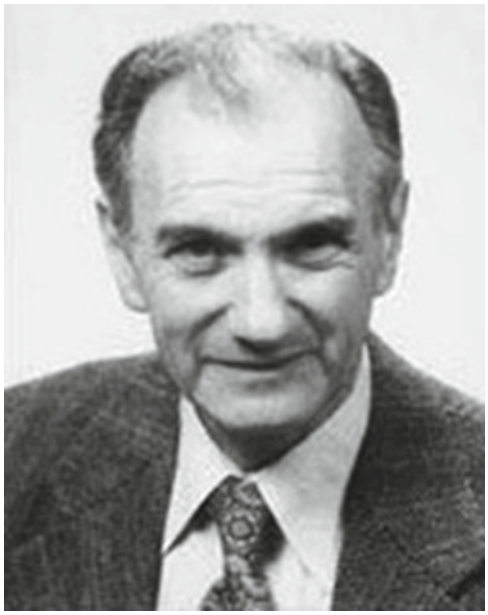
Joel Elkes



Joel Elkes is a psychiatrist who has been instrumental in the study of pharmacology for the treatment of psychiatric disorders and the study of neurotransmitter receptors. Elkes was born in Königsberg, Germany in 1913. He received his medical training at St. Mary's Hospital in London, earning his degree in 1941. After rotations in orthopedic surgery, ophthalmology, and internal medicine at St. Mary's and time spent in the USA, Elkes was appointed head of the Department of Experimental Psychiatry at the University of Birmingham, the first of its kind. The department included laboratories for animal experimentation as well as a clinical unit. It was here that Elkes along with his wife conducted the first blind controlled trial of chlorpromazine in patients with chronic psychosis. In 1957, Elkes moved to the USA where he set up a clinical neuropharmacological research center (CNRC) at St. Elizabeths Hospital in Washington DC. At the CNRC, important research on dopamine metabolism and the action of the serotonin receptor agonist tryptamine was performed, along with important clinical investigations by Fritz Freyhan and Anthony Hordern. He pioneered the study of receptorology, the study of neurotransmitter effects on different types of receptors in the brain. From 1963 until his retirement in 1974, Elkes was Chair of the Department of Psychiatry at Johns Hopkins University. He changed its name to the Department of Psychiatry and Behavioral Sciences to reflect his belief that psychiatry provided a bridge between medicine and the behavioral sciences. He later worked at McMaster University and the University of Louisville.

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Jean-Étienne Dominique Esquirol

Jean-Étienne Dominique Esquirol was born in Toulouse, Occitania, France in 1772. In 1799, he worked at the Salpêtrière Hospital in Paris and became a student of Philippe Pinel. Esquirol established a maison de santé or private asylum in 1801 or 1802. Esquirol believed that the origin of mental illness lies in the passions of the soul and was convinced that madness does not fully and irremediably affect a patient's reason. Esquirol saw the question of madness as institutional and national. This was especially true for the poor where he saw the state, with the help of doctors, playing an important role. He also saw an important role for doctors in caring for people accused of crimes who were declared not responsible by reason of insanity.

In 1817, Esquirol initiated a course in maladies mentale at the Salpêtrière, the first formal teaching of psychiatry in France. In 1818, he published articles describing the conditions in which the insane lived throughout France. These articles constituted a program of reform directed both at the government and the medical profession: first, that insanity should be treated in special hospitals by physicians with special training; second, that reform involved exporting the advances made in Paris to the provinces; third, that 'a lunatic hospital is an instrument of cure.' By this he meant that the physical structure of new psychiatric hospitals must be designed to support the practice of the new specialty; and fourth, Esquirol insisted on the definitive medicalization of the care of the insane. In 1822, he was appointed inspector general of medical faculties, and in 1825 director of Charenton Hospice. He became the main architect of the national law of 1838 that instituted departmental asylums for all needy French mental patients and that is still in force today. He died in 1840.

Esquirol's 1838 text, Mental Maladies, was the outstanding psychiatric text of the time. In this text, he differentiated between hallucination (a term he coined) and illusion. He classified insanities into monomania—a partial insanity identified with affective disorders—and general delirium-like mania. He also delineated conditions such as kleptomania, nymphomania, and pyromania. Through his observations on people within the asylums, epileptics were distinguished from the insane.

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Rosalind Franklin

Rosalind Elsie Franklin was a British physical chemist and crystallographer who was best known for her contribution to understanding of the fine structure of DNA. Since Franklin had died in 1958, she was not eligible for the Nobel Prize given to Crick, Watson, and Wilkins in 1962. Her experimental data were instrumental in subsequent work by Crick and Watson to build their model of DNA in 1953. She also led work on tobacco mosaic and polio viruses. Her significant contribution to the discovery of DNA structure has impacted our understanding of heredity in etiopathology of all psychiatric disorders.

Rosalind Franklin was born in London, England in 1920 and was enrolled at St. Paul's Girls' School. Hoping to study physical science, she passed the entrance examinations of Cambridge University. In 1938, she entered Newnham College. After graduating from Cambridge in 1941, she spent a year doing research in physical chemistry with future Nobel Prize winning chemist, Ronald Norrish. In a time span of 4 years, Franklin published five papers on coals and carbons, and eventually that work earned her a Ph.D. from Cambridge University in physical science in 1945. In 1951, Franklin started to work as a research associate at King's College London in the Medical Research Council's Biophysics Unit, directed by Sir John Randall. In 1952, Rosalind Franklin worked with Raymond Gosling at improving the X-ray pictures of DNA they had produced. In 1953, Francis Crick and James Watson published their model of the double-helical structures of DNA in Nature on April 25, with a small footnote to Franklin's data. In 1953, Franklin moved to Birkbeck College to use X-ray crystallography to study the structure of the tobacco mosaic virus. In 1956, on a trip to the USA, she began to suspect a health problem. In September of the same year, an operation revealed two tumors in her abdomen. She continued to work and released 13 papers in 2 years and fell ill for the last time on March 30th, 1958 and died on April 16th of the same year from ovarian cancer.

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Daniel Carleton Gajdusek

Gajdusek was an American physician and medical researcher of Slovakian-Hungarian descent, who was the corecipient (along with Baruch S. Blumberg) of the Nobel Prize in Physiology or Medicine in 1976 for work on kuru, the first prion disease discovered.

Gajdusek was born in 1923 and graduated in 1943 from the University of Rochester (New York), where he studied Physics, Biology, Chemistry and Mathematics. He obtained an M.D. from Harvard University in 1946. He performed postdoctoral research at Columbia, Caltech, and Harvard before being drafted to complete military service at the Walter Reed Army Medical Service Graduate School as a research virologist. He held a position at the Institute Pasteur in Tehran from 1952 to 1953, where he was excited by the challenges “offered by urgent opportunistic investigations of epidemiological problems in exotic and isolated populations.” In 1954, he went to work as a visiting investigator at the Walter and Eliza Institute of Medical Research in Melbourne. It was here he began the work that culminated in the Nobel prize. He received the award in recognition of his study of a remarkable disease, kuru (Fore word for "trembling"). This disease was rampant among the South Fore people of New Guinea in the 1950s and 1960s. Gajdusek correctly connected the prevalence of the disease with the practice of funerary cannibalism, practiced by the South Fore. With elimination of this practice, Kuru disappeared among the South Fore within a generation. Gajdusek died in 2008.

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Irving I. Gottesman

Irving Gottesman is an American psychologist, known for his research on the interaction of genetic and environmental factors in the onset and expression of psychopathological conditions. Gottesman, in 1967, was the first psychologist to apply the polygenic and threshold models of inheritance to psychopathology. His methodological approach and conductance of twin-studies have become the standard in the field and provided undeniable evidence that genetics plays a determining factor in schizophrenia. Additionally, he has advanced the concepts of epigenetics and endophenotypes in genetic studies of major psychiatric disorders.

After receiving his PhD in psychology from the University of Minnesota in 1960, Gottesman worked at the Institute of Psychiatry in London where he first began his study of the incidence of schizophrenia among Danish twins. He was later a professor at the University of Virginia and the University of Minnesota. Gottesman has received numerous awards including the Joseph Zubin award from the Society for Research in Psychopathology, the 2001 American Psychiatric Association award for Distinguished Scientific Contributions and more recently the Gold Medal of the American Psychological Association.

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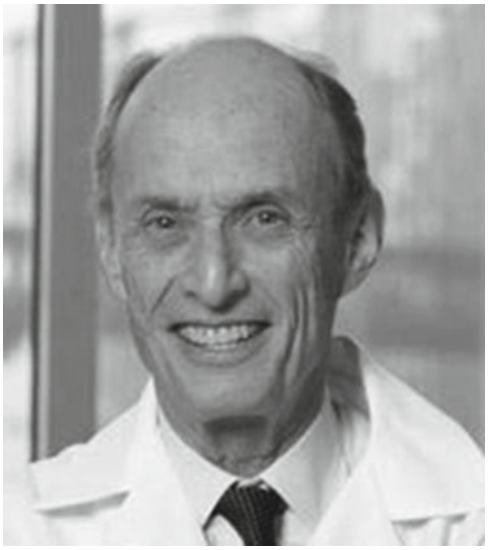
Paul Greengard



Paul Greengard is an American neuroscientist and professor of molecular and cellular neuroscience at Rockefeller University in New York. He was one of three winners who shared the 2000 Nobel Prize for Physiology or Medicine for their discoveries concerning signal transduction in the brain. Greengard's research showed that the neurotransmitter dopamine interacts with neurons to increase cyclic AMP, activating a protein kinase A (PKA) that via phosphorylation, can signal the cell to make new proteins increasing the number of neurotransmitter receptors in the synapse. Dopamine pathophysiology has been implicated in a number of disorders including schizophrenia, Parkinson's disease, attention deficit disorder, and drug abuse. His work facilitates the development of new drugs for the treatment of neurological and psychiatric disorders.

Greengard was born in 1925 and raised in New York City and attended public schools in Brooklyn and Queens. During World War II, he served in the Navy and was involved in developing an early-warning system to intercept Japanese kamikaze planes. After his service, he attended Hamilton College in New York on the G.I. bill and graduated in 1948 with a degree in mathematics and physics. He had been interested in pursuing graduate school in physics but opposed the field's focus on nuclear weapons and instead turned his studies to the new field of biophysics. Greengard has written that he had hoped to use his mathematics and physics knowledge to solve biological problems. He completed his graduate studies at Johns Hopkins University and did his postdoctoral work at the University of London, Cambridge University and University of Amsterdam. He worked as a professor at Albert Einstein College of Medicine, Vanderbilt University, and Yale University. He is currently Vincent Astor Professor at Rockefeller University where he has worked since 1983. Greengard used his Nobel Prize honorarium—almost $400,000, to fund the Pearl Meister Greengard Prize, an award for outstanding women scientists named after his mother and established in 2004.

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Wilhelm Griesinger

Wilhelm Griesinger was a German psychiatrist who was one of the first proponents of the biological basis of mental illness or biological psychiatry. Griesinger was born in Stuttgart and obtained his medical training at the University of Tübingen. In the 1840s through the 1850s, Griesinger traveled extensively holding positions throughout Germany, Paris, Vienna, as well as serving as the director of the medical school in Cairo. In 1845, he published his landmark textbook *Mental Pathology and Therapeutics*, in which he proposed that mental illnesses are based on brain-based disorders. A second textbook, *The Pathology and Treatment of Mental Illnesses*, which was published in 1861, expanded on his ideas of the brain as the center for mental illnesses. In addition, in 1868, he founded the influential psychiatric journal *Archive of Psychiatry and Nervous Diseases* in collaboration with Ludwig Meyer and Carl Friedrich Otto Westphal. Griesinger was also a reformer in the treatment of patients with psychiatric disorders. The existing system in use at the time housed patients with mental illnesses in rural asylums. Griesinger proposed moving patients to urban settings, to help integrate them back into society. To this extent, he proposed short-term hospitalization combined with cooperation with the patient's natural support systems. He died in 1868, in Berlin.

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Johann Bernhard Aloys von Gudden

Johann Bernhard Aloys von Gudden was a German neuroanatomist and psychiatrist, who was born in Kleve in 1824. He completed his medical studies in 1848 and subsequently worked at a number of psychiatric institutions. In 1855, he became director of the Werneck Psychiatric Hospital where he mandated a humane, no-restraint policy which allowed for social interaction among the patients. At the time, outer ear hematomas and fractured ribs were identified as common in psychiatric patients. Rather than being physical symptoms of their disorders, Gudden found that these were a result of neglect and violent action on the part of the staff at psychiatric hospitals. In 1869, Gudden succeeded Wilhelm Griesinger to become the Director of the Burghölzli Psychiatric Hospital. In 1872, he became the director of the Upper Bavarian District Mental Asylum and a Professor of Psychiatry at the University of Munich. At Munich, he continued neuroanatomical studies of the brain that he had begun at Werneck and Zurich. Using the technique of secondary degeneration (also known as "Gudden's method") Gudden described the interconnections between the cortex and subcortical areas. Gudden also developed a microtome for sectioning the human brain and described anatomic centers. Among other techniques pioneered by Gudden included new methods of staining of brain tissue sections, and the use of lesions in the nervous systems of newborn animals and studying the resultant changes in the brain. Both Franz Nissl and Emil Kraepelin worked in Gudden's laboratory. Later, Gudden worked as a psychiatrist for members of the Bavarian Royal family including Prince Rudolf and later King Ludwig II. In 1886, immediately following the arrest of King Ludwig, Gudden drowned in Starnberg Lake in what may have been either an accidental drowning or a murder.

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James F. Gusella

James F. Gusella is a Canadian geneticist who mapped the Huntington's disease gene to chromosome 4. Gusella was born in Ottawa and received his Ph.D. in biology from the Massachusetts Institute of Technology in 1980. He then established his own laboratory at Massachusetts General Hospital (MGH). Huntington's disease is characterized by poor muscle coordination, cognitive impairments and behavioral abnormalities and the emergence of symptoms typically occurs between the ages of 35–45. There is also progressive neuronal cell loss in the caudate and putamen. Gusella mapped the Huntington's Disease gene to chromosome 4 via somatic cell hybridization in population samples from the USA and Venezuela. The gene was isolated in 1993. Gusella's pioneering work stimulated similar research in genetics to identify genes by their chromosomal positions. In 2003, he was named the director of the MGH Center for Human Genetic Research. Gusella is also the Bullard Professor of Neurogenetics at the Department of Genetics at Harvard University and the Director of the Harvard Medical School Center for Neurofibromatosis and Allied Disorders.

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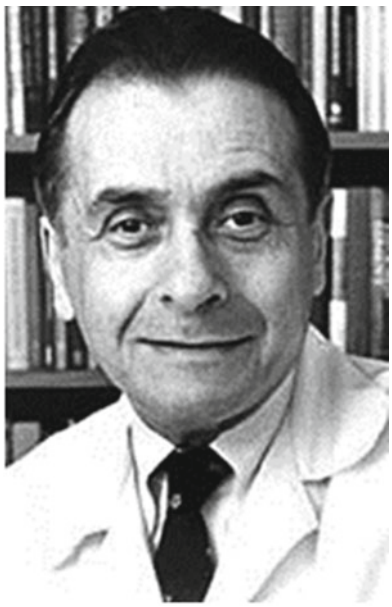
Samuel Guze



Samuel Guze was an American psychiatrist who, along with other faculty at Washington University School of Medicine developed the "medical model" of psychiatry in which psychiatric illness is diagnosed as any other physical illness—through the use of a scientific model and criteria. A textbook for use of the Washington University approach was published by Guze and colleagues in 1974: *Psychiatric Diagnosis*. In 1980, Guze and his colleagues helped to create the American Psychiatric Association's DSM-III diagnostic classification of mental disorders. In addition to developing the medical model of psychiatry, Guze was involved in areas of research including criminality, the relationship between sociopathy and hysteria and alcoholism. His work on hysteria was significant not only in and of itself but because through it, he introduced the use of a standard interview. Guze's work on alcoholism provided important findings about the genetic vulnerability to alcoholism.

Guze was born in 1923 in New York City and graduated from Washington University School of Medicine at the age of 21 in 1945. After serving for 2 years in the Army Medical Corps, Guze returned to Washington University and aside from 1 year of medical training in Connecticut in 1949 remained at Washington University for the rest of his career. Guze was a faculty member in internal medicine beginning in 1951 and psychiatry beginning in 1955. He served as Vice-Chancelor for Medical Affairs and President of the Washington University Medical Center from 1971 to 1989, department head for psychiatry from 1975 to 1989 and 1993–1997. Throughout his career Guze received many awards and honors including the Gold Medal Research Award from the Society of Biological Psychiatry and the Distinguished Public Service Award from the US Department of Health and Human Services. He died in 2000.

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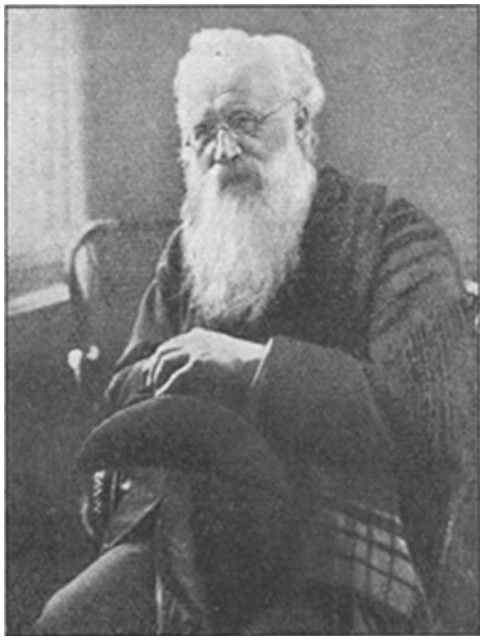
Ewald Hecker



Ewald Hecker was a German psychiatrist who developed the concept of hebephrenia. Hecker was born in Halle in 1843. Following his medical education, he worked with Karl Ludwig Kahlbaum at the mental hospital at Görlitz until 1872. During his time at Görlitz, Hecker developed the concepts of hebephrenia and cyclothymia. He described hebephrenia as a disorder that originates during adolescence, characterized by disorganized behavior and speech and a decline in mental function. This represented one of the first descriptions of schizophrenia and today hebephrenia is considered as a subtype of schizophrenia. Cyclothymia was characterized as a mood disorder that cycled between depression and mania, a forerunner to the concept of bipolar disorder. In developing the idea of discrete mental disorders, Hecker along with Kahlbaum refuted the idea of unitary psychosis (i.e., the idea that all psychiatric symptoms were related to a single mental disorder) which was the prevalent view of mental illness at the time. This research paved the way for later classification of psychiatric disorders. In 1891, he opened his own mental hospital in Wiesbaden. Here, Hecker established a more humane environment for patients with mental disorders. He died in 1909.

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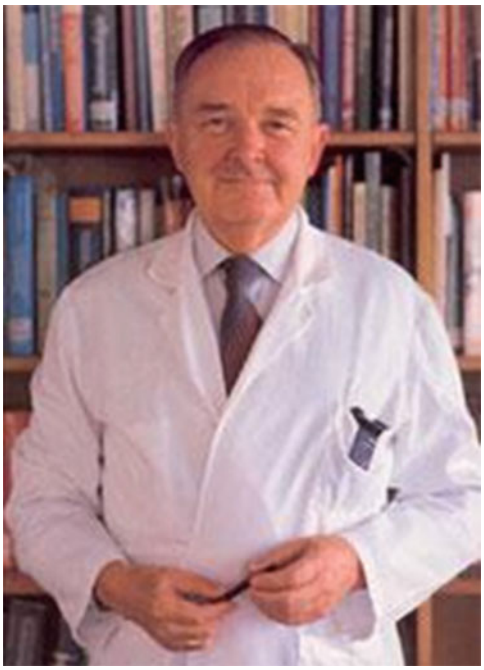
Paul Janssen



Paul Janssen was a Belgian pharmacologist who along with his research team developed over 70 compounds, most notably haloperidol. Haloperidol, first introduced in 1959, has remained 56 years later one of the most effective and reliable substances to treat schizophrenia and manage psychosis. Following the development of haloperidol, Janssen and his research team developed another 13 antipsychotic agents including pimozide, bromperidol, and risperidone that have contributed greatly to the treatment of psychiatric patients. Of the 70 compounds developed by Janssen, four are included on the World Health Organization's list of essential drugs: (haloperidol, levamisole, miconazole, and mebendazole).

Janssen was born in 1926 in Turnhaut, Belgium. He received his medical degree in 1951 from the University of Ghent. Following graduation Janssen worked as a physician with the Belgian army and began his studies of medical chemistry and pharmacology, joining his father's pharmaceutical company in 1953. By age 27 he was the president of the company and introduced research and development to what had been a manufacturing company. During his lifetime Janssen published more than 850 journal articles. He died in 2003.

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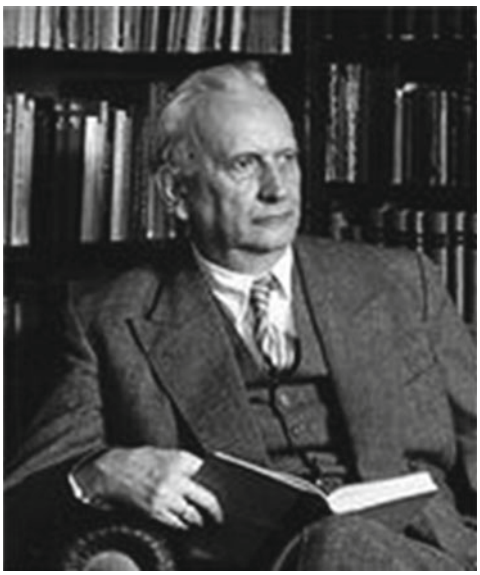
Karl Jaspers



Karl Jaspers was a German psychiatrist who furthered the field of psychiatry by proposing that illnesses be diagnosed according to form, not content. He argued that a patient experiencing psychosis should be diagnosed not by the content of their delusion, but by the way in which the belief is held. He also introduced the *biographical method* of study, which consisted of detailed life histories of patients with mental illness and notes describing how patients themselves felt about their symptoms. Jaspers published his views on mental illness in two volumes of work entitled, *General Psychopathology*, which have become a classic in psychiatric literature and laid the foundation for many current diagnostic criteria.

Jaspers was born in 1883, completed his medical training in 1909 and took a position at a psychiatric hospital in Heildelberg, Germany where Emil Kraepelin had previously worked a few years earlier. In 1913, he left clinical practice to take a post teaching psychology at Heidelberg University. At age 40 his interests turned from psychology to philosophy, where he returned to develop themes found in his early psychiatric works. His philosophic works were rooted in existentialism and explored the theme of individual freedom. His works *Philosophy* and *Transcendence* both became internationally known and secured his place in the philosophical community until his death in 1969.

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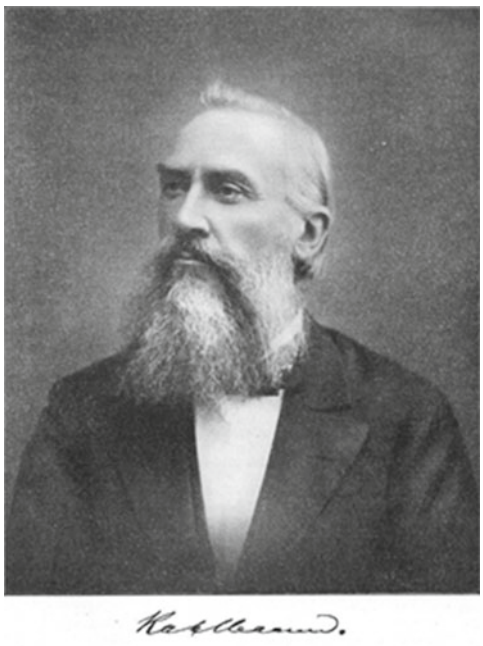

Karl Ludwig Kahlbaum was a German psychiatrist who is known for his work with catatonia. Kahlbaum was born in 1828 in Dirschau, Germany (now Tczew, Poland). He studied medicine at the Universities of Königsberg, Würzburg, and Leipzig before receiving his degree in Berlin in 1855. He subsequently worked as a physician at an asylum in Wehlau and as a lecturer at the University of Königsberg. In 1867, he became the medical director of the mental hospital at Görlitz, a position he held until his death in 1899.

While working at Görlitz, Kahlbaum began a reclassification of mental disorders based on: (1) essential features such as symptom patterns; and (2) associated features such as age of onset, course of the disease, family history, and outcome. Along with colleagues such as Ewald Hecker, Kahlbaum introduced terms such as dysthymia, cyclothymia, catatonia, paraphrenia, and hebephrenia to classify mental disorders. This classification system would prove to be influential on Emil Kraepelin and his concept of dementia praecox. Kahlbaum first described catatonia in an 1874 publication *Catatonia or Tension Insanity*. Kahlbaum described several symptoms of catatonia including mutism, immobility, a fixed gaze, a lack of reaction to sensory stimuli, and that catatonia was sometimes accompanied by waxy flexibility. He described the syndrome as being transient or chronic and stressed the notion of the epileptiform nature of catatonic attacks. Kraepelin later incorporated catatonia as a subtype of dementia praecox.

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Franz Josef Kallmann

Franz Josef Kallmann was a German-American psychiatrist who pioneered the study of psychiatric genetics. He was born in 1897 in Neumarkt, Germany (now part of Poland) and received his medical degree in 1919 from the University of Breslau. Kallmann worked at the psychiatric institute of the University of Berlin, where he also studied psychoanalysis and neuropathology. Kallmann later worked at a psychiatric research institute in Munich. In 1936, Kallmann fled the Nazi regime and settled in the USA. He joined the staff at the New York State Psychiatric Institute where he became the chief of psychiatric research in medical genetics. Additionally, he served as head of medical genetics at Columbia-Presbyterian Medical Center. In 1948, he was one of the founding members of the American Society for Human Genetics and the American Journal of Human Genetics. During his career, Kallmann coauthored 176 peer-reviewed articles and became president of the American Psychopathological Association. He died in 1965.

In 1929, Kallmann began his familial studies of psychiatry with the hypothesis that schizophrenia was an inherited condition. He performed a study that examined the rate of schizophrenia among the siblings and children of people diagnosed with the disorder. In all, he obtained information on 13,851 subjects, of which 1,087 were test subjects. In 1938, he published his work, *The Genetics of Schizophrenia*, based on his research and concluded that schizophrenia was a recessive, heritable condition. He calculated that there was a 16.8% risk of developing schizophrenia among the children of subjects with schizophrenia compared with a 0.85% risk in the general population. Further, he conducted twin studies in the USA and identified a 69% risk for an identical twin to develop schizophrenia if the other twin was diagnosed with the disorder. Kallmann also identified a genetic condition now known as Kallmann's syndrome in which there is a failure to start or fully complete puberty, with symptoms of hypogonadism, infertility, and an altered sense of smell.

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Eric R. Kandel

Eric Richard Kandel is an Austrian born psychiatrist, neuroscientist, and professor of biochemistry and biophysics at Columbia University in New York. He was one of three recipients of the 2000 Nobel Prize in Physiology or Medicine for his groundbreaking research on the physiological basis of memory storage in neurons. His corecipients were Paul Greengard and Arvid Carlsson. Using the nervous system of a sea slug as an experimental model, he demonstrated how changes in synaptic function are central for learning and memory. In his collaboration with Greengard, he delineated the role of cAMP-dependent protein kinase (PKA), in the formulation of long-term memory. Further research at his laboratory at Columbia University revealed that the activation of a control protein, CREB (cAMP response element binding protein) increased the number of synaptic connections implicit in long-term memory. His life work lead to the current understanding that short-term memory is associated with functional changes in existing neuronal connections, while long-term memory is associated with protein synthesis and change in the number of synaptic connections.

Kandel was born in 1926 in Vienna, Austria to parents of East Polish decent. In 1939, he and his family were driven out of Europe by Nazi Germany and immigrated to Brooklyn, New York. He was accepted to Harvard University on scholarship and majored in 20th century European history and literature. His interest in psychiatry was born out of a friendship with a colleague friend whose parents were psychoanalysts. Kandel has written that the insights about unconscious mental processing offered by psychoanalysis rooted his interest in the biology of motivation and memory. In order to become a psychoanalyst, he entered medical school at New York University. By graduation he was firmly interested in the biology of the brain and began his research in basic neural science at Columbia University. His residency training in psychiatry was completed at Harvard University, and he did postdoctoral training at the National Institute of health and at the Insitut Morey in Paris. He is the founding director of the Center for Neurobiology and behavior at Columbia University, a member of the National Academy of Sciences and has received numerous honors including the National Medal of Science.

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Leo Kanner

Leo Kanner was an American psychiatrist who was a pioneer in the field of child and adolescent psychiatry and was the first to characterize autism. Kanner was born in Klekotow in then Austria-Hungary (now part of Ukraine) in 1896. He received his medical degree from the University of Berlin in 1921. In 1924, he immigrated to the USA to work at the State Hospital at Yankton County, South Dakota (where the Leo Kanner Memorial Building was dedicated in 1980) as an assistant physician. In 1930, he was selected to develop the first department of child psychiatry at Johns Hopkins University where he became an Associate Professor of Psychiatry in 1933. In 1935, he published his textbook *Child Psychiatry*, the first publication to focus on this topic in English. In 1943, in a landmark paper, Kanner described 11 children who displayed symptoms of not being able to relate to others and an insistence on sameness, especially with regard to their environment. Furthermore, he noted that 8 out of the 11 children acquired language significantly later than normal. He termed his findings "autistic disturbances of affective contact," later known as infantile autism or Kanner's syndrome. Throughout his career, Kanner was a defender of children with intellectual disability, at a time when most psychiatrists excluded them from their clinics. Kanner received the Stanley Dean Award in 1965. After retiring from Johns Hopkins, Kanner continued as an active consultant and served as a Visiting Professor at The University of Minnesota, University of Wisconsin, and Stanford University. He died in 1981.

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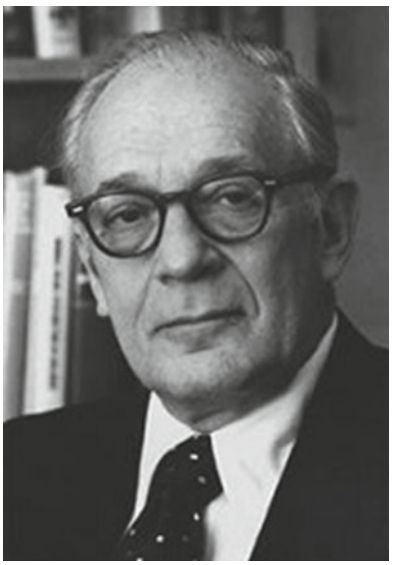
Seymour S. Kety



Seymour S. Kety was an American neuroscientist who applied principles of basic science to the study of human behavior and disease. Kety developed a technique to study cerebral blood flow (CBF). Later, during experiments of the feline visual system Kety combined these techniques with autoradiography to demonstrate increases in CBF in the visual pathways, thus providing the first examples of functional brain imaging. As a result, he revolutionized the study of cognitive, emotional, and mental processes. Kety also studied the genetics of schizophrenia and developed a methodological approach for separating the genetic and environmental contributions to schizophrenia. In collaboration with Danish scientists, Kety examined the biological and adoptive family lines of schizophrenics who had been adopted at birth. This work provided definitive evidence for involvement of genetic factors in the etiology of schizophrenia.

Kety was born in 1915 and received his MD from the University of Pennsylvania. While still a medical student, Kety developed a process to use citrate to treat lead poisoning. After a fellowship at Harvard University where he studied traumatic shock and became interested in CBF he returned to the University of Pennsylvania where he developed his techniques for measuring CBF. In 1950, he was appointed as Scientific Director of the Intramural Research Programs of the National Institute of Mental Health (NIMH), despite his not being a psychiatrist, in order to ensure sound, rigorous research. In 1967, Kety accepted an appointment at Harvard as chief of the Laboratories of Psychiatric Research. Kety's research earned him election to the National Academy of Sciences, numerous honorary degrees and awards including the Lasker Special Achievement Award in Medical Science in 1999. He died in 2000.

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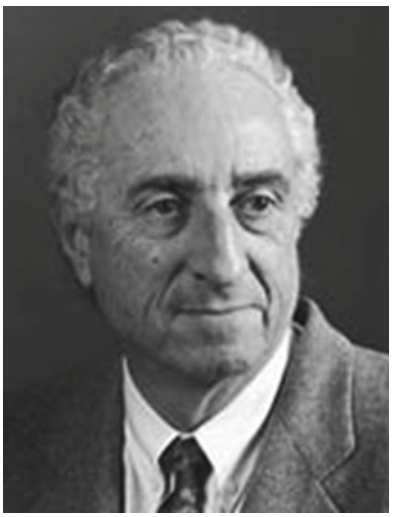
Donald F. Klein



Donald F. Klein was born in 1928 in New York City. Throughout his career he has made significant contributions to psychiatric nosology and pharmacology. Klein received his medical degree in 1952 from the State University of New York Downstate Medical Center College of Medicine and trained as a psychiatrist at Creedmoor State Hospital in New York and at the US Public Health Service Narcotics Hospital in Lexington, Kentucky. In 1962, while working as a psychiatrist at Hillside Hospital in Glen Oaks, New York, he performed a randomized placebo-controlled trial which compared the efficacy of chlorpromazine vs. imipramine (the first tricyclic antidepressant) for the treatment of major depression. He found that chlorpromazine was just as effective as imipramine, suggesting that antipsychotic and antidepressant medications may not be as distinct as was thought at the time. In a separate study, he also found that imipramine prevented panic attacks in subjects who were hospitalized with agoraphobia, although it did not resolve anxiety or phobic avoidance. Based on these findings and others, Klein proposed that patterns of drug response could be used to help delineate psychiatric disorders. In 1969, he coauthored the first book on clinical psychopharmacology, *Diagnosis and Drug Treatment of Psychiatric Disorders*, with John M. Davis. His work has helped to clarify our understanding of ADHD, schizophrenia, unipolar and bipolar depression, and social phobia. His work in classifying anxiety disorders by separating panic disorder and agoraphobia from generalized anxiety disorder, social phobia, and simple phobia has been especially influential. Klein was a lead coauthor of the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM-III*), in 1980. He is currently a Senior Scientific Advisor at the Child Mind Institute in New York City.

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Sergei Korsakoff

Sergei Korsakoff was a Russian psychiatrist who studied the effects of alcohol on the nervous system and identified a form of dementia now known as Korsakoff's syndrome. Korsakoff was born in 1854 in Gus-Khrustanly, Russia. He studied medicine at Moscow University, graduating in 1875. He worked at the Preobrazhensky psychiatric hospital where he began his studies of the effects of alcohol on the nervous system, publishing his thesis *Alcoholic Paralysis* in 1887. He then became head of the psychiatric clinic at Moscow University. He died in 1900 of heart failure.

Korsakoff identified a form of psychosis in subjects with alcoholism, which is now known to be a result of thiamine (vitamin B_1) deficiency in the brain. Korsakoff's syndrome can also be a result of severe malnutrition as well as chemotherapy, dialysis, eating disorders, or age. As a result of this deficiency, there is neuronal loss, gliosis, and atrophy of mammillary bodies. These morphological features underlie the main symptoms of Korsakoff's syndrome: anterograde amnesia, retrograde amnesia, confabulation, impaired conversational ability, lack of insight, and apathy. In 1891, prior to Kraepelin's concept of dementia praecox, Korsakoff introduced the concept of "dysnoia" or paranoia, which could be considered a precursor of acute schizophrenia. Finally, Korsakoff was a proponent of rights of those with psychiatric disorders including avoiding restraints on patients as well as ending the practice of isolation, the use of straight jackets, and forced sterilization.

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Emil Kraepelin

Emil Kraepelin was a German psychiatrist who is often credited with being the founder of modern psychiatry. His distinction between "dementia praecox" (later renamed schizophrenia by Bleuler) and "manic-depression" (bipolar disorder) represented a paradigm shift in the practice of psychiatry. Kraepelin held the conviction that psychiatric illnesses are caused by biological and genetic disorders and opposed the approach of Sigmund Freud who viewed and treated mental disorders as secondary to psychological factors.

Kraepelin proposed psychiatric diseases be grouped together based on common *patterns* of symptoms (as was done in internal medicine) rather than simply by the similarity of symptoms, as was the standard prior to his work. Drawing on his long-term observation of patients, he developed the criteria of course, outcome and prognosis of mental illness. During much of the twentieth century Kraepelin's contributions were marginalized due to the success of Freudian theories of mental illness. However, his fundamental concepts on the etiology and diagnosis of psychiatric disorders form the basis of all major diagnostic systems used today, most notable the American Psychiatric Association's DSM-5 and the World Health Organization's ICD system.

Kraepelin was born in 1856 in Germany. Having chosen a career in psychiatry at the young age of 18, Kraepelin began researching the influence of acute medical diseases on psychiatric illness as a third year medical student. He completed his medical training in Wurzburg, Germany and went on to a position at the Munich Clinic where he studied brain anatomy, learning, and memory. He was given his first chairmanship at age 30 in Dorpat (at that time a part of Russia, now in Estonia) and went on to chairs at both Heidelberg and Munich, where he was later joined by Nissl and Alzheimer with whom he collaborated. He died in 1926.

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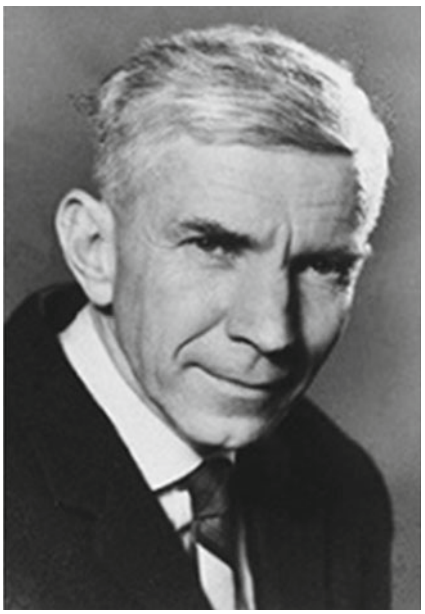
Roland Kuhn



Roland Kuhn was a Swiss psychiatrist who \first identified the antidepressant properties of imipramine. Kuhn was born in 1912 in Biel Switzerland. He received his medical training in Bern and Paris, earning his M.D. in 1937. In 1939, Kuhn joined the staff at the psychiatric hospital in Münsterlingen, where he spent his entire career, serving as director from 1960–1980. For his contributions to psychiatry, Kuhn received honorary doctorates from the universities of Louvain, Basel, and the Sorbonne. He died in 2005.

Kuhn originally requested new antipsychotic drugs from the pharmaceutical manufacturer Geigy to use at the Münsterlingen psychiatric hospital. Geigy sent a compound G22355. While testing G22355's efficacy in patients with schizophrenia, Kuhn found that the drug was not effective in treating symptoms of schizophrenia and in many cases worsened psychosis. However, Kuhn noted that in patients with schizophrenia and depression, G22355 resolved their depressive symptoms. Kuhn then tested it for a three-week trial in patients with depression and found it was effective in treating their symptoms. Kuhn published the results of his study in 1957 and in 1958 his findings were confirmed in a second study in Montreal conducted by Heinz Lehmann. G22355 was later named imipramine and was the first tricyclic antidepressant medication. Kuhn's pioneering discovery of imipramine's antidepressant action revolutionized pharmacotherapy of depression.

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Charles Philippe Leblond

Charles Philippe Leblond was a Canadian cell biologist/histologist who, in collaboration with L.F. Bélanger, developed the process of radioautography (also known as autoradiography) whereby radioactive isotopes are used to localize labeled molecules in tissues. Leblond employed this now universally used technique to investigate and describe the dynamic processes of cell growth, differentiation and migration in most actively dividing tissues of the body including teeth, long bones, spermatozoa, thyroid tissue, gastrointestinal cells, and neurons and glial cells.

Leblond was born in Lille, France in 1910 and received his medical degree from the University of Paris in 1934. Following a 2-year stay at Yale University as a Rockefeller Fellow, Leblond went to McGill University where he taught histology. During World War II, he joined the Free French army. Leblond returned to the Department of Anatomy at McGill as an associate professor, becoming department chair in 1957 a position he served until 1974. Leblond received numerous awards for his research including a fellowship of the Royal Society of Canada in 1951 and a fellowship of Royal Society of London in 1965. In 1977, he was appointed Officer of the Order of Canada. He died in 2007.

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Charles Philippe Leblond. Protoplasm 1991;160:3.

Rita Levi-Montalcini

Rita Levi-Montalcini was a developmental biologist who, along with Stanley Cohen, discovered nerve growth factor (NGF). In 1952, Levi-Montalcini demonstrated that when mouse tumors were transplanted to chick embryos they produced robust neurite outgrowth. This outgrowth was specific for sensory and sympathetic nerves. Direct contact was not needed to induce such growth, indicating that a chemical was being released by the tumors. Through additional experiments in collaboration with Stanley Cohen, NGF was isolated and characterized. The discovery and characterization of NGF provided an important mechanism to explain how nerves grow and reach their targets. NGF has since been studied extensively, providing insight into cell growth and survival, wound healing as well as pathologies such as muscular dystrophy or dementia.

Rita Levi-Montalcini was born in 1909 and received her medical degree from the University of Turin in 1936. Her academic career was cut short in 1938 by the introduction of laws barring Jews from academic and professional careers. During World War II, Levi-Montalcini conducted experiments in a small laboratory at her home. In 1946, she took a position in the laboratory of Professor Viktor Hamburger at Washington University in St. Louis where she carried out her work on NGF. She was appointed a full professor at Washington University in 1958 and established a research unit in Rome in 1962. Levi-Montalcini was the recipient of many awards and honors for her work on NGF including induction into the US National Academy of Sciences in 1968 and the Nobel Prize for Physiology or Medicine (along with Stanley Cohen) in 1986. She died in 2012.

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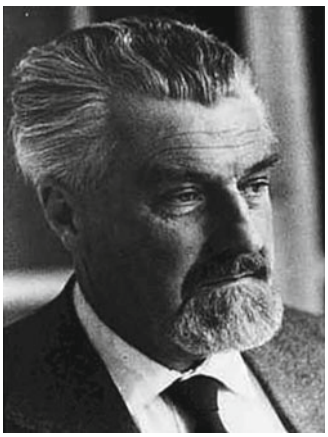
Konrad Zacharias Lorenz



Konrad Lorenz was born in 1903 in Austria and trained as a zoologist, animal behaviorist, and ornithologist. Lorenz studied instinctive behavior in animals, especially in greylag geese and jackdaws. Working with geese, he rediscovered the principle of imprinting.

In 1940, he became a professor of psychology at the Immanuel Kant University in Königsberg. He was drafted into the Wehrmacht in 1941. He sought to be a motorcycle mechanic, but instead he was assigned as a medic. He was a prisoner of war in the Soviet Union from 1944 to 1948. The Max Planck Society established the Lorenz Institute for Behavioral Physiology in Buldern, Germany, in 1950.

He shared the 1973 Nobel Prize in Physiology or Medicine "for discoveries in individual and social behavior patterns" with two other important early ethologists, Niko Tinbergen and Karl von Frisch. Together with Nikolaas Tinbergen, Lorenz developed the idea of an innate releasing mechanism to explain instinctive behaviors (fixed action patterns). Influenced by the ideas of William McDougall, Lorenz developed this into a "psychohydraulic" model of the motivation of behavior.

Konrad Lorenz is probably best known for his 1973 book, Civilized Man's Eight Deadly Sins, in which he addresses the following paradox: All the advantages that man has gained from his ever-deepening understanding of the natural world that surrounds him, his technological, chemical and medical progress, all of which should seem to alleviate human suffering… tends instead to favor humanity's destruction. He died in 1989.

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Ladislas Joseph Meduna

Ladislas Joseph Meduna was a Hungarian neurologist who delineated the antagonism between epilepsy and schizophrenia and developed the first treatment of seizures for schizophrenia. On January 23, 1934, Meduna induced a seizure in a 33-year-old man with severe catatonic schizophrenia. After just five treatments, the catatonia and psychosis resolved. In 1939, he published *Die Konvulsionstherapie der Schizophrenie*, in which he described the recovery of greater than 50% of 110 schizophrenic patients treated by pentylenetetrazol-induced seizure. Prior to his work, schizophrenia was considered to be a heritable, incurable condition.

Early in his career, Meduna first conceived of the antagonism between epilepsy and schizophrenia when he observed that patients with epilepsy had a higher concentration of brain glia than those with schizophrenia. He found that patients with schizophrenia had a low co-occurrence of epilepsy, and that 16.5% of epileptic patients who became psychotic had a remission of their seizures. Additionally, he noted anecdotal reports of patients whose schizophrenia was "cured" with the development of epilepsy. Meduna's work lead to the discovery of the safer electroconvulsive therapy, which still stands today as one of the most reliable and effective treatments for the severely mentally ill.

Meduna was born in 1896, received his medical degree in Budapest in 1922 and was appointed to the Hungarian Interacademic Institute for Brain Research where he researched the structure and pathology of the pineal gland prior to his clinical research as Professor of Neurology at Loyola University after emigrating in 1938. After WWII, he continued his research at the Illinois Psychiatric Institute. In 1950, he wrote *Oneirophrenia*: *the Confusional State*, which described dream and fugue states in psychosis, and in 1953, he served as president of the Society of Biological Psychiatry. He maintained a private practice until his death in 1964.

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Herbert Y. Meltzer

Herbert Meltzer is an American psychiatrist and pharmacologist known for his work on the mechanism of action of antipsychotic and antidepressant drugs and the role of dopamine and serotonin in the etiology and treatment of schizophrenia. Meltzer's work on the action of clozapine resulted in a pivotal study that led to its approval for use in the USA. Meltzer's research demonstrated that clozapine was effective in reducing the risk of suicide in schizophrenics and that it improved cognition. Additionally, his research on clozapine led him to develop a general theory of how to create an antipsychotic drug with minimal or no extrapyramidal side effects which in turn was integral in the development of second generation antipsychotics such as olanzapine and risperidone. Meltzer's research continues to test the hypothesis that specific serotonin and dopamine receptor subtypes are important to the mechanism of action of antipsychotic drugs.

Meltzer received his M.D. from Yale University 1963 and received his psychiatric training at the Massachusetts Mental Health Center. Meltzer has been professor of psychiatry at the University of Chicago, Case Western Reserve University and the Vanderbilt University School of Medicine. Currently, he is a professor of psychiatry and behavioral sciences, pharmacology, and physiology at Northwestern University. Meltzer has received much recognition for his research including the Gold Medal Award of the Society of Biological Psychiatry and the Stanley Dean Award of the American College of Psychiatry.

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Emmanuel J. M. Mignot

Emmanuel Mignot is a French psychiatrist who has identified the gene that causes narcolepsy. Mignot was born in Paris and received his Ph.D. in pharmacology from the Pierre and Marie Curie University and his M.D. from the Rene Descartes School of Medicine in 1985. Mignot completed an internship and residency at Necker Enfants Malades Hospital in Paris. Since 1989 he has been the Director of the Center for Narcolepsy, and since 2010 the Director of Center for Sleep Sciences and Medicine at Stanford University. He is also a Professor of Psychiatry. Mignot is an Elected Member of the Institute of Medicine, received the Outstanding Achievement Award from the Sleep Research Society, and the W. Alden Spencer Award from the Columbia University College of Physicians and Surgeons.

Through 10 years of study, beginning in 1989, Mignot and colleagues identified the gene that causes narcolepsy in dogs—hypocretin receptor 2. Furthermore, in 2000, Mignot in collaboration with Seiji Nishino of Stanford University and Gert Jan Lammers of the Leiden University Medical Center found that hypocretin 1 levels were absent in the cerebrospinal fluid of patients with narcolepsy and that this deficiency was the cause of narcolepsy. More recent research has demonstrated the presence of CD4+ T-cells reactive to hypocretin, establishing an autoimmune basis for narcolepsy.

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António Caetano de Abreu Freire Egas Moniz

Antonio Caetano de Abreu Freire Egas Moniz was born in Portugal in 1874 and trained as a psychiatrist and neurosurgeon. In 1927, he developed cerebral angiography, the technique of using X-rays to visualize arteries and veins that are transiently opacified with the injection of a high density agent. This procedure would allow physicians to map blood vessels in and around the brain, permitting the diagnosis of several kinds of neurological disorders, such as tumors and arteriovenous malformations. He received the Oslo Prize for this discovery. The method is widely used today for the diagnosis of brain tumors and vascular diseases in the brain and other organs.

In 1936, Moniz and his associate Almeida Lima developed for the first time a surgical technique to interrupt the nerve fibers which connect the thalamus (a relay for sensory information coming into the brain) to the prefrontal cortex (already known at the time as a brain structure involved in higher intellectual functions of the brain, and in emotions, as well). He was the inventor of prefrontal leucotomy which was changed to lobotomy by American surgeons who introduced a larger severing of the neural fibers. It was used as a surgical approach to the radical treatment of several kinds of mental diseases by use of several types of psychosurgery. For this work, Moniz received the Nobel Prize in 1949, jointly with the Swiss neurophysiologist Walter Rudolf Hess. He died in 1955.

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Franz Nissl

Franz Nissl was a German neuropathologist who is best known for developing a staining technique that allows for the selective visualization of neuronal cell bodies. What became known as the Nissl stain is basic aniline which stains RNA blue. The rough endoplasmic reticulum, individual ribosomes and the nucleus are all labeled by this method. This technique greatly increased the ability to study neuropathology of the brain by allowing for the correlation of mental and nervous diseases with observable changes in brain tissue. During his later years, Nissl examined the connections between the cerebral cortex and the thalamus. His Nissl technique continues to be used in pathological staining of brain sections even to this day.

Nissl was born in 1860 and received his doctorate from the University of Munich is 1885. In 1889, he went to Frankfurt to work at the Städtische Irrenanstalt where he did much of his pioneering work in collaboration with Carl Weigert. It was there he also met Alois Alzheimer and frequently collaborated with him. In 1895, he moved to the University of Heidelberg at the invitation of Emil Kraepelin. He died in 1919.

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Hideyo Noguchi

Hideyo Noguchi was a Japanese bacteriologist who discovered that the spirochete that causes syphilis, *Treponema pallidum*, was present in the nervous system of deceased patients. Noguchi demonstrated the presence of the bacteria in the cerebral cortex of patients that had died from conditions not previously linked with syphilis. His work demonstrated that *T. palladium* invades the nervous system as the disease progresses. Noguchi studied other diseases as well, most notably yellow fever, which he proved to be a viral disease.

Noguchi was born in Japan in 1876 and received his medical degree from Tokyo Medical College in 1897. In 1899, he emigrated from Japan to the USA working first at the University of Pennsylvania and then in 1904 at the Rockefeller Institute for Medical Research (now Rockefeller University). It was at the Rockefeller Institute that Noguchi performed his experiments with *T. pallidum* and the nervous system. While studying yellow fever in Accra in what is now Ghana, Noguchi contracted the disease and died in 1928. Noguchi has been honored posthumously both by Ghana and Japan by having his image appear on a stamp and since 2004, his image has appeared on the 1,000 Yen note.

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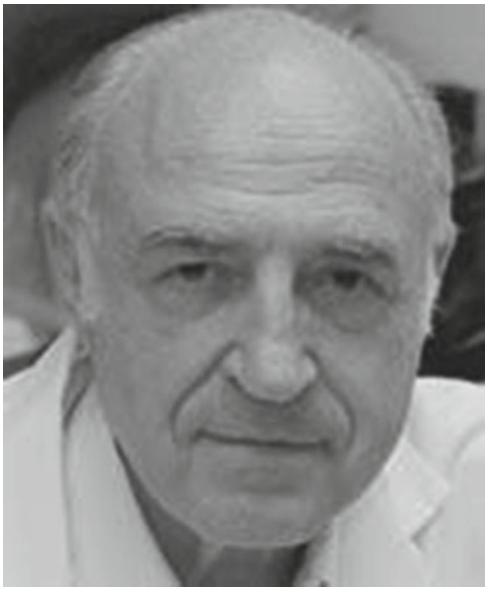
John William Olney



John William Olney was an American psychiatrist and neuropathologist who characterized the role of glutamate in neurotransmission and neurodegenerative diseases. His early work established glutamate as a key excitatory neurotransmitter important for normal brain function. Olney also discovered that glutamate could have a neurotoxic effect, as too much glutamate stimulation was shown to destroy nerve cells a condition he referred to as "excitotoxicity." Through subsequent research Olney identified excitotoxicity as a mechanism which causes neurodegeneration seen with acute brain injury including stroke and trauma. More recent research focused on a role for excitotoxicity in chronic neuropsychiatric disorders including Alzheimer's disease and schizophrenia.

Olney was born in 1931. After receiving his medical degree from the University of Iowa in 1963, Olney joined Washington University as a resident in 1964. He became a full professor of psychiatry and neuropathology in 1977. Olney received many awards and honors throughout his career including the Wakeman award, Society of Biological Psychiatry Lifetime Achievement Award, and the membership of the Institute of Medicine of the National Academy of Sciences. He died in 2015.

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Paul Patterson

Paul Patterson was an American neuroscientist and developmental biologist who performed pioneering experiments on neural plasticity and co-developed an important mouse model of schizophrenia and autism. Patterson was born in 1943 and received his Ph.D. from Johns Hopkins in 1970 and later became a professor in the Department of Neurobiology at Harvard University. In 1983, he joined the faculty at the California Institute of Technology where he was the Anne P. and Benjamin F Biaggini Professor of Biological Sciences. Patterson was instrumental in developing Caltech's MD/PhD program which allowed Caltech students to earn their Ph.D. at Caltech and their M.D. at either UCLA or USC. He died in 2014.

During his postdoctoral fellowship, Patterson developed a technique for growing peripheral nerve cells in culture. He made the groundbreaking finding that mature peripheral nerve cells could change their identity in response to environmental stimuli. Thus, their identity was not absolute and genetically determined. Later, he found that levels of leukemia inhibitory factor were responsible for the changes in neural cell differentiation. Patterson was also involved in co-developing an animal model for schizophrenia by investigating the impact of environmental factors, namely, prenatal viral infection, on the development of schizophrenia-like phenotype in the exposed offspring. Using viral mimetic poly I:C, Patterson and colleagues found impairments in prepulse inhibition of the acoustic startle response and latent inhibition that are similar to what is observed in subjects with schizophrenia. Further, he found changes in the offspring of mothers that were administered Poly I:C who demonstrated decreased sociability, impaired communication, and increased repetitive behavior, all of which reproduce core symptoms of autism.

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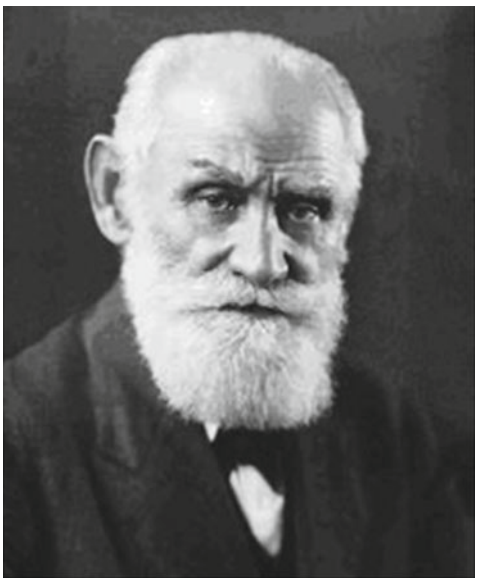
Ivan Petrovich Pavlov



Pavlov was a Russian physiologist, psychologist, and physician. He was awarded the Nobel Prize in Physiology or Medicine in 1904 for research pertaining to the digestive system. Pavlov is widely known for first describing the phenomenon now known as classical conditioning in his experiments with dogs.

Ivan Pavlov was born in 1849 in Ryazan, Russia. He began his higher education as a seminary student, but dropped out and enrolled in the University of St. Petersburg to study the natural sciences. He received his doctorate in 1879.

In the 1890s, Pavlov was investigating the gastric function of dogs by externalizing a salivary gland so he could collect, measure, and analyze the saliva produced in response to food under different conditions. He noticed that the dogs tended to salivate before food was actually delivered to their mouths, and set out to investigate this "psychic secretion," as he called it. He thereby established the basic laws for the establishment and extinction of what he called "conditional reflexes"—i.e., reflex responses, like salivation, that only occurred conditionally upon specific previous experiences of the animal. He died in 1936.

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Philippe Pinel

Regarded by many as the father of modern psychiatry, Pinel was born in Saint-André, Tarn France in 1745. After receiving a degree from the faculty of medicine in Toulouse, he studied an additional 4 years at the Faculty of Medicine of Montpellier. In August 1793, Pinel was appointed "physician of the infirmeries" at Bicêtre Hospital. At the time it housed about 4,000 imprisoned men–criminals, petty offenders, syphilitics, pensioners, and about 200 mental patients. Pinel's patrons hoped that his appointment would lead to therapeutic initiatives. While at Bicêtre Pinel did away with bleeding, purging, and blistering in favor of a therapy that involved close contact with and careful observation of patients. Pinel visited each patient, often several times a day, and took careful notes over 2 years. He engaged them in lengthy conversations. His objective was to assemble a detailed case history and a natural history of the patient's illness.

Pinel developed a new classification of mental illnesses—mania, melancholia, idiocy, and dementia—and stated that these were caused mainly by heredity and influences from the environment. Through an asylum regimen of education, reasoning, and persuasion, many symptoms of insanity could be alleviated. This was the moral treatment of insanity. He died in 1826.

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Pasko Rakic

Pasko Rakic is a Yugoslavian-born neuroscientist who discovered the molecular mechanisms governing neuronal migration. His research has focused on the interaction of neuronal and glial cells during neuronal migration, first identifying the location, time-course and, most importantly, the mechanisms by which immature nerve cells acquire their position and identity in the brain. Subsequently, Rakic identified important molecules involved in the guided migration by neurons. This research has not only helped to explain development of the central nervous system but also brain pathology in autism and schizophrenia. Rakic's research has also provided insight into developmental plasticity by discovering that neurons overproduce projections, synapses and signaling molecules which are later selectively pruned back due to competitive interactions.

Rakic was born in 1933 and received his medical and graduate training at the University of Belgrade. He began his research career at Harvard University in 1962, moving to Yale University in 1978 where he still maintains an active research laboratory. In 2003, he received the 15th Annual Bristol-Myers Squibb Neuroscience Award.

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Eli Robins

Eli Robins was an American psychiatrist who, along with colleagues at Washington University School of Medicine, was critical to the establishment of diagnostic criteria for psychiatric disorders and is known for his pioneering work on suicide. The St. Louis (Feighner) criteria for psychiatric illness later evolved into the DSM-III and now the DSM-5. Together with George Murphy, Robins launched the first systematic study of suicide, using a systematic interview of relatives, physicians, coworkers and so forth to gather information on the person who had committed suicide. This process was later defined as a "psychological autopsy" of the deceased. A key finding of their work was that over 90% of suicide victims had some form of mental illness, usually depression or alcoholism.

Robins was born in Rosenberg, Texas in 1921. He received his medical degree from Harvard University in 1943. Robins spent his career at the Washington University Department of Psychiatry, becoming a professor in 1958 and serving as chairman of the department from 1963 to 1975. Robins authored more than 175 peer-reviewed articles and his honors included the Gold Medal of the Society for Biological Psychiatry and the Paul Hoch Award of the American Psychiatric Association. He died in 1994 after a long battle with multiple sclerosis.

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Kurt Schneider

German psychiatrist Kurt Schneider worked to improve psychiatric diagnosis and in the tradition of Kraepelin and Jaspers, believed that diagnosis should be based on the symptomatic pattern of illness, rather than the content of a sign or symptom. In an attempt to differentiate schizophrenia from other forms of psychosis, Schneider developed a list of characteristic symptoms, which have become known as "Schneiderian First and Second Rank Symptoms." These include audible thoughts, voices heard arguing, voices commenting on one's activities, thought insertion, thought withdrawal, thought broadcasting, belief that an external force is acting on the body, and delusional perceptions (ideas of reference). Although the reliability of "fist rank symptoms" for diagnosis of schizophrenia has since been questioned, these terms are still used broadly by psychiatrists.

Schneider was born in 1887 and received his medical training in Berlin and Tübingen and in 1931 became director of the Psychiatric Institute in Munich, which was founded by Kraepelin. At odds with the rising influence of psychiatric eugenics championed by the Nazi Party, he left the institute and served as an army physician during World War II. After the war, when anti-Nazi professors were appointed to rebuilt German medical facilities, Schneider was appointed as Dean of the Medical School at Heidelberg University where he remained until his retirement in 1955. He died in 1967.

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Philip Seeman

Philip Seeman was born in Winnipeg, Canada in 1934. He received an M.D. from McGill University (1960). He had a rotating internship at Detroit's Harper Hospital, and subsequently received his Ph.D. from Rockefeller University in Life Sciences in 1966. In 1966, he was a Postdoctoral Fellow at the University of Cambridge. Since 1967 he has been at the University of Toronto, Department of Pharmacology, and served as its Chairman between 1977 and 1987. He is currently emeritus professor of pharmacology and psychiatry.

Philip Seeman spent 12 years searching for a target common to the action of all antipsychotic drugs. At first he discovered that the antipsychotics were anesthetic-like membrane stabilizers, but the concentrations were higher than that which occur in the spinal fluid in antipsychotic-treated patients. In 1977, he discovered the antipsychotic dopamine receptor, now called the dopamine D2 by employing radioactively labeled haloperidol. After discovering the D2 receptor, he measured (in postmortem human brain tissues) the sharp rise of D2 receptors in early age, followed by the slow fall of D2 receptors over the life-span. These data have been confirmed by positron emission tomography (PET).

Seeman's second major finding was to discover that atypical antipsychotics such as clozapine (Clozaril) and quetiapine (Seroquel) dissociated from the D2 receptor very quickly, in contrast to traditional antipsychotics such as haloperidol (Haldol) or chlorpromazine (Thorazine), which remained on the D2 receptor for much longer duration. The different time course helps explain one of the bases of atypical antipsychotic action, a principle essential in designing better antipsychotic medication.

A third discovery by Philip Seeman is his recent finding that the basis of dopamine supersensitivity is consistently associated with a marked increase in the proportion of D2 receptors that are in a state of high affinity for dopamine (so-called $D2^{High}$ receptors). This is important because up to 75% of patients with schizophrenia are supersensitive to dopamine-like drugs (methylphenidate or amphetamine) at doses that do not affect control individuals. This elevation of $D2^{High}$ receptors occurs in all animal models of psychosis and the proportion of $D2^{High}$ receptors is dramatically increased, by 200–900%. These elevated $D2^{High}$ states appear to serve as the final common pathway for many injuries to the brain, whether by lesions, drugs, or gene alteration. These $D2^{High}$ states, therefore, appear to be directly related to the psychotic signs and symptoms in patients. This interpretation is compatible with the fact that D2 blockade is an effective treatment for psychotic signs and symptoms, even though cognitive difficulties may remain.

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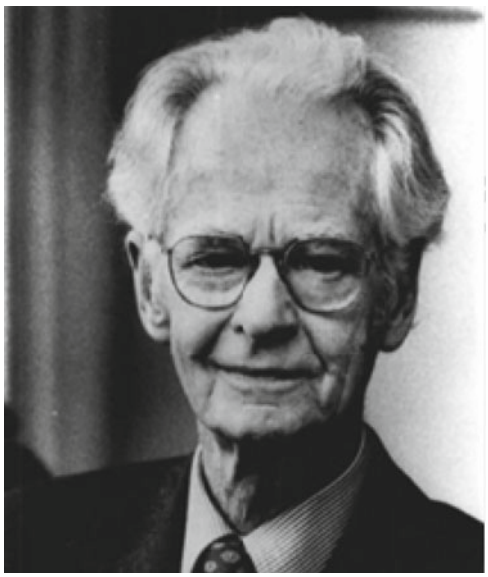
B. F. Skinner



Burrhus Frederick Skinner was an American psychologist and author best known for his pioneering work in experimental psychology. Skinner was an advocate of behaviorism which is based on the idea that everything an organism does (including thinking and feeling) can be considered behaviors. Skinner performed pioneering work on the use of operant conditioning to change behaviors. Operant conditioning uses consequences to modify the occurrence of specific behaviors. Originally studied by Edward L. Thorndike, Skinner elaborated on the idea to create a more detailed theory based on reinforcement (a consequence that causes a behavior to increase in frequency), punishment (a consequence that causes a behavior to decrease in frequency) and extinction (the lack of a consequence following any behavior leading over time to occur less frequently).

Skinner was born in 1904 in Pennsylvania and received a PhD from Harvard University in 1934. It was at Harvard where Skinner began his pioneering work on operant conditioning. His studies were later compiled in his first book, *The Behavior of Organisms*. In 1936, he joined the faculty at the University of Minnesota and later in 1945, the University of Indiana, returning to Harvard in 1948 where he would remain for the rest of his career. In 1968 Skinner received the National Medal of Science and in 1971 was awarded the Gold Medal of the American Psychological Association. He died of leukemia in 1990.

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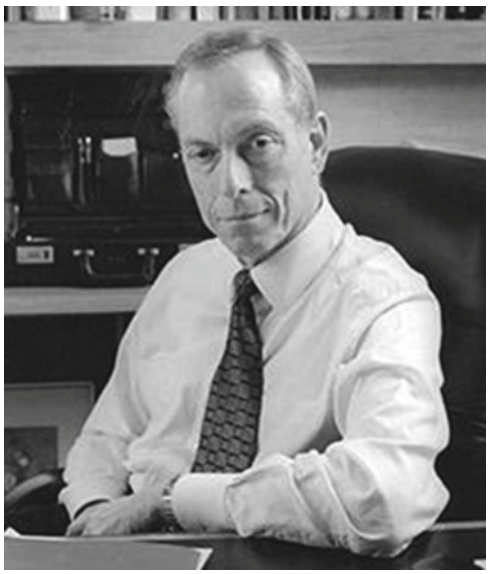
Solomon Snyder



Solomon Snyder is an American psychiatrist and neuroscientist known for his pioneering work in the field of molecular neuroscience as it pertains to mental illness. Snyder has identified receptors for neurotransmitters and drugs including the adenosine receptor, opiate receptor, bradykinin receptor as well as several receptors for serotonin and codiscovered the dopamine receptor. In addition to receptors, Snyder has identified novel neurotransmitters including the gases nitric oxide and carbon monoxide and D-amino acids including D-serine which have altered previously held notions of neurotransmission. Snyder's pioneering techniques have enabled the discovery of novel psychiatric drugs for the treatment of psychiatric disorders.

Snyder was born in 1938 and received his medical degree from Georgetown Medical School in 1962 at the age of 23. From 1963, he worked in the laboratory of Julius Axelrod at the National Institute of Mental Health. In 1965, he went to Johns Hopkins University, becoming a full professor in 1970 in both pharmacology and experimental therapeutics. In 1980, Snyder was appointed the director of the Department of Neuroscience, a position which he held until 2006. He has received numerous awards including the Lasker Award in 1978 for his work on opiate receptors and the National Medal of Science in 2003.

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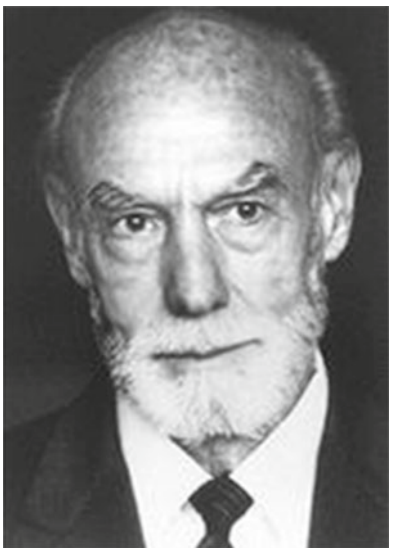
Roger W. Sperry



Roger Sperry was an American neurobiologist whose work contributed to the understanding of the lateralization of brain function. Sperry had the opportunity to work with epileptics who had undergone commissurotomy, a severing of the connections between the left and right hemispheres of the brain which had been demonstrated to cause a reduction in symptoms without any obvious changes in behavior. Sperry and colleagues, tested the patients using tasks known to be dependent on functions of each hemisphere. He found that each hemisphere contained certain consciousness:

> "indeed a conscious system in its own right, perceiving, thinking, remembering, reasoning, willing, and emoting, all at a characteristically human level, and…both the left and the right hemispheres may be conscious simultaneously in different, even in mutually conflicting, mental experiences that run along in parallel."

Sperry demonstrated that the isolated left hemisphere is concerned with abstract thinking and the logical analysis of details, whereas the right hemisphere is concerned with, among other things, spatial consciousness and the comprehension of complex relationships.

Sperry was born in 1913 and received a PhD in zoology from the University of Chicago in 1941. After serving at the University of Chicago in the departments of anatomy and psychology, Sperry joined the department of psychobiology at California Institute of Technology in 1954, where he worked until his retirement. In 1981, he shared the Nobel Prize in Physiology or Medicine with David Hubel and Torsten Wiesel. He died in 1994.

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Baruch Spinoza

Baruch Spinoza was a Dutch philosopher whose posthumously published *Ethics*, which is generally regarded as his magnum opus, contains one of the first modern analyses of human emotions. Much like classical Stoicism, Spinoza's philosophy offered a therapeutic basis for obtaining happiness. However, whereas the Stoics believed that reason could defeat emotion, Spinoza postulated that only a stronger emotion could defeat or displace another emotion. Spinoza also held that emotions be detached from external cause in order to master them.

Additionally, Spinoza distinguished between active emotions (those that are rationally understood) and passive emotions (those that are not). Understanding of the true causes of passive emotions could transform them into active emotions. Taken together, Spinoza's distinct ideas about emotions influenced 20th century psychological techniques.

Spinoza was born in Amsterdam in 1632, of Portuguese Jewish parents. A lens crafter by trade, Spinoza first gained infamy as a philosopher for his positions that defied Jewish law, ultimately leading to his being issued a writ of *cherem* (excommunication). Spinoza began to publish his works in the 1650s and 1660s and made a name for himself as a philosopher. However, the unfavorable reaction to his anonymously published *Theologico-Political Treatise* led him to abstain from publishing further. It was only after his death in 1677 that his works including the *Ethics* were published by friends.

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Robert Spitzer

Robert Spitzer was an American psychiatrist who contributed significantly to the classification of psychiatric disorders through his work in organizing the *Diagnostic and Statistical Manual of Mental Disorders III* (*DSM-III*). Spitzer was born in White Plains, New York and received his medical degree from New York University School of Medicine in 1957. He trained in psychiatry at the New York Psychiatric Institute and in 1961 became a research fellow in the biometrics department. There, Spitzer codeveloped the Mood Disorder Questionnaire (MDQ) which is used to diagnose bipolar disorder and the Patient Health Questionnaire, a screening tool to identify mental illness. He also developed a computer program called DIAGNO I in 1968 which could derive a diagnosis based on answers to the Psychiatric Status Schedule. Spitzer was one of four members of the US Steering Committee for the USA–UK Diagnostic Project, which examined differences in diagnosis between the two countries. A key finding was that the diagnosis of schizophrenia was broader in the USA than the UK where certain patients would have been diagnosed as manic-depressive or bipolar rather than schizophrenic. In 1973, Spitzer provided a leadership role to have homosexuality removed from the American Psychiatric Association's list of mental disorders. Spitzer served as the chair for the task force that produced the DSM-III, which revolutionized the way psychiatric disorders were classified using discrete categories and specific diagnostic criteria. He also chaired the task force that revised the DSM-III, publishing the DSM-III-R in 1987. Spitzer retired in 2010 after a 49-year career in psychiatry. He died in 2015.

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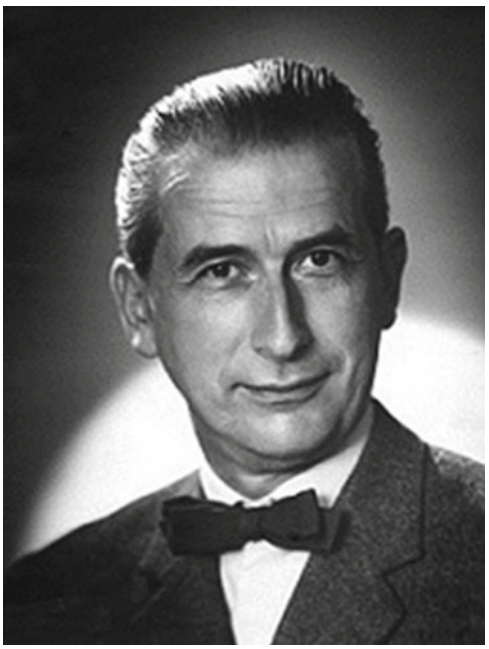
Erik Ströemgren



Erik Ströemgren was a Danish psychiatrist who pioneered epidemiological studies of psychiatric disorders as well as the use of lithium. Ströemgren was born in 1909 in Copenhagen where his father was an astronomy professor at the university. He studied medicine at Copenhagen University, earning his medical degree in 1934. Beginning in 1933, Ströemgren worked on an epidemiologic study of psychiatric illness in the residents of Bornholm island. The isolated location and distinct dialect of the residents, suggested an ideal population for such a study. Making more than 1,000 home visits, and using modern techniques including taking family histories and calculating prevalence rates for psychiatric disorders, the resulting publication—*Contributions to Psychiatric Genetics on the Basis of an Island Population*—published in 1938, remains a classic in the field. In 1945, he became the chief of the Aarhus psychiatric hospital at Risskov as well as a professor of psychiatry at Aarhus University. It was here that Ströemgren was involved in further epidemiologic studies, including the 5-year census studies, and national and international family, twin, and adoption studies that significantly contributed to our understanding of psychiatric genetics. While at Risskov, Ströemgren was also involved in the first placebo-controlled studies of lithium to treat mania. He retired in 1979. 50 years after his initial study at Bornholm, Ströemgren revisited the surviving members of the original proband families with the intention of publishing a follow-up study. Unfortunately, he died in 1993 before he was able to complete his work.

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Thomas Südhof

Thomas Südhof is a neuroscientist whose work has focused on defining the mechanisms that govern neurotransmitter release. Südhof was born in Göttingen, Germany in 1955. He received his M.D. and Ph.D. from the University of Göttingen in 1982. He began his career in research as a postdoctoral fellow at the University of Texas Southwestern Medical School and later started his own laboratory in 1986. Südhof worked at UT Southwestern for over 20 years where he began his pioneering work on presynaptic neurons and neurotransmitter release. He was the founding chair of the Department of Neuroscience at UT Southwestern and has been an Investigator of the Howard Hughes Medical Institute since 1986. In 2008, Südhof moved to Stanford University where he is currently the Avram Goldstein Professor in the School of Medicine and Professor by Courtesy, of the Departments of Neurology and Psychiatry and Behavioral Sciences. In 2013, Südhof was awarded the Nobel Prize in Medicine for his research.

Südhof began investigating the presynaptic neuron when most research focused on the postsynaptic neuron and its role in learning and memory. Südhof focused on the mechanisms of neurotransmitter release and identified synaptotagmins, which in response to Ca^{2+} influx into the presynaptic cell, mediate neurotransmitter release. He further identified scaffolding proteins known as RAB3A interacting molecules (RIMs) that are vital to active zone function and Munc13s which are essential for synaptic transmission. Additionally, Südhof identified neurexins and neuroligins, which are presynaptic and postsynaptic proteins, respectively, that form physical connections between presynaptic and postsynaptic cells allowing for neurotransmission to take place. Mutations in these proteins result in abnormal synaptic function which have been identified in subjects with autism and schizophrenia.

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Earl W. Sutherland Jr.

Earl Sutherland was an American biochemist who first discovered and characterized cAMP as a second messenger. Sutherland studied the mechanism of glycogen degradation in the liver in response to epinephrine. Sutherland discovered that epinephrine activated the enzyme phosphorylase responsible for breaking down glycogen to glucose and that this activation was carried out by an intermediate which he termed the second messenger (with epinephrine being the first messenger). The second messenger was later identified as cyclic adenosine monophosphate or cAMP. This work provided a generalized mechanism for the action of many hormones. Rather than hormones entering the cell directly, hormones bind to the surface leading to an activation of cAMP or other second messenger on the inside of the cell, activating or inhibiting various cellular processes.

Sutherland was born in 1915 and received his medical degree from Washington University in St. Louis in 1942. After serving as a doctor during World War II, Sutherland returned to Washington University where he was a researcher in the laboratory of Carl Cori. In 1953, he became the chair of the department of pharmacology at Case Western Reserve University where he did his work on cAMP for which he was awarded the Nobel Prize for Physiology or Medicine in 1971. He later moved to Vanderbilt University in 1963 where he worked until retiring in 1973. In addition to the Nobel Prize, Sutherland was elected to the National Academy of Sciences in 1966 and received the National Medal of Science in 1973. He died in 1974.

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Edwin Fuller Torrey

Edwin Fuller Torrey is an American psychiatrist whose research laid the groundwork for the idea of schizophrenia as a biologically based illness. He is generally considered to be the proponent of the infectious etiology for schizophrenia. Prior to his research the focus on schizophrenia was that it was a result of "bad parenting." Much of Torrey's work has focused on the parasite *Toxoplasma gondii* (TG). TG is able to establish persistent infection in the central nervous system and cause neurological and psychiatric symptoms in some of those infected. Torrey has proposed that infection by TG either prenatally or postnatally, could contribute to the etiology of schizophrenia.

In addition to his research, Torrey is also known for his advocacy on behalf of schizophrenics. He is a founder of the Treatment Advocacy Center which supports outpatient commitment for patients who are not likely to survive safely in the community without supervision and for many years was an advisor to the National Alliance on Mental Illness. Torrey is also the Associate Director of Research of the Stanley Medical Research Institute which is the largest private provider of research on schizophrenia and bipolar disorder in the USA.

Torrey was born in 1937 and received his medical degree from McGill University. He has received two commendation medals from the US Public Health Service and a research award from the International Congress on Schizophrenia.

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Andreas Vesalius

Andreas Vesalius (Andreis van Wesel) was a Flemish anatomist and physician who is often cited as the father of modern human anatomy. He was born in 1514 in Brussels. Vesalius studied medicine at the Universities of Louvain and Paris and received his medical degree from the University of Padua in 1537. He was a lecturer at the University of Padua until he became the court physician to Charles V and later Charles's son Phillip II. In 1564, while returning from a pilgrimage to Jerusalem, his ship wrecked in the Ionian Sea on the island of Zakynthos, where he died.

Vesalius is notable for reviving the practice of human dissection, despite a ban on the practice by the Catholic church. He made the discovery that the work of the Greek physician Galen, who was considered the authority on human anatomy, was wholly based on animal dissections (primarily pigs and Barbary apes). Vesalius published his highly influential book on human anatomy, *The Structure of the Human Body*, in 1543, which refuted many of Galen's claims. He also published an abridged version of his book for medical students and revised it in 1555. Vesalius provided a detailed description of brain anatomy. Among his findings in the nervous system was that the nerve is the unit responsible for transmitting sensation and motion and that nerves stemmed from the brain. At the time, it was thought that ligaments and tendons had the functions of nerves and that nerves originated in the heart. Through studies of the optic nerve, Vesalius also posited that nerves were not hollow.

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Oskar Vogt

Oskar Vogt was a German neurologist whose work in brain anatomy greatly influenced neuroscientific research. Vogt was born in Husum in 1870 and received his medical doctorate from the University of Jena in 1894. Vogt then worked as an intern at Jena, as well as at the Burghölzli asylum in Zurich, with additional positions in Leipzig and Paris. In Paris, Vogt met his wife Cécile Vogt-Mugnier, who was also a neurologist. They married in Berlin in 1899 and opened a neurological laboratory, eventually establishing the Neurobiologisches Universitäts-Laboratoirum in 1915. Based on his renown, Vogt was sought as a consultant on Vladimir Lenin's illness and, following Lenin's death, Vogt received Lenin's brain for histological studies. Vogt noted a large number of "giant cells," later identified as unusually large cortical pyramidal cells, which he concluded was a sign of superior mental function. With the advent of the Nazi regime, Vogt was dismissed from his current position as director of the Kaiser-Wilhelm-Institut für Hirnforschung, although Vogt and his wife continued their research independently until Vogt was drafted to work at military hospitals. Following the war, Vogt continued his work until his death in 1959.

Vogt, along with his wife, performed pioneering work in the study of neuroanatomy of the brain, particularly the cortex, thalamus, and basal ganglia. Vogt and his colleagues defined a six layer pattern of the cerebral cortex (contrasting with the five-layer model of Theodor Meynert and the seven-layer model of Ramon y Cajal). Additionally, they published a paper in 1941 which represented an important partitioning and naming of thalamic structures. Later, in 1948, they described pathological changes of the thalamus in patients diagnosed with schizophrenia. Oskar and Cécile Vogt revised the description of the basal ganglia, using the term striatum to describe, collectively, the caudate nucleus, and the nucleus accumbens.

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Nora Volkow

Nora Volkow is a psychiatrist who has performed crucial imaging studies that have helped clarify the basis of drug addiction. Born in Mexico, Volkow received her medical degree from the National Autonomous University of Mexico in 1980 and completed her residency in psychiatry at New York University. Volkow worked at Brookhaven National Laboratory in Upton, New York where she held several appointments including Associate Chief of Staff of the Clinical Research Center, Director of Nuclear Medicine, and Chairman of the Medical Department. Volkow has also been a Professor of Psychiatry and Associate Dean of the medical school at the State University of New York-Stony Brook. In 2003, she became Director of the National Institute on Drug Abuse (NIDA). Volkow has published 580 peer-reviewed articles and has received numerous awards in recognition of her research including the Joel Elkes International Award for Clinical Research from the American College of Neuropsychopharmacology, the Paul Abersold Award from the Society for Nuclear Medicine, and the International Prize from the French Institute of Health and Medical Research.

Volkow has pioneered the use of brain imaging techniques to study drug addiction. She has demonstrated changes in brain structure that occur with drug abuse which also help explain why drug addiction is so difficult to overcome. In particular changes in activity in the prefrontal cortex (PFC) with regard to attention, working memory, inhibitory control, decision making, and motivation have been shown in drug-addicted individuals vs. controls. Importantly, Volkow and colleagues have demonstrated that activity in the orbitofrontal cortex, which is involved in decision making, and the anterior cingulate cortex, which is involved in reward and decision making is reduced in addicted individuals. This reduction in activity is associated with reduced dopaminergic function. Recent work has found that methylphenidate, an indirect dopamine agonist normalizes activity in mesolimbic circuits, and enhances executive function which may provide a way to help treat drug addiction.

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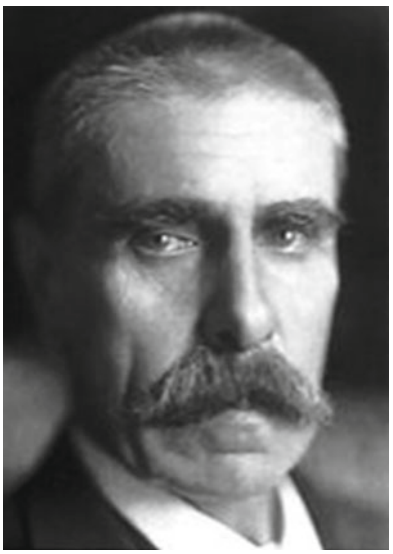
Julius Wagner-Jauregg



Julius Wagner-Jauregg was born in 1857 in Austria and studied medicine at the University of Vienna from 1874 to 1880, where he also studied with Salomon Stricker in the Institute of General and Experimental Pathology, obtaining his doctor's degree in 1880. In 1889, he succeeded the famous Richard von Krafft-Ebing at the Neuro-Psychiatric Clinic of the University of Graz, and started his research on goiter, cretinism, and iodine.

The main work pursued by Wagner-Jauregg throughout his life was related to the treatment of mental disease by inducing a fever. In 1887, he investigated the effects of febrile diseases on psychoses, making use of erysipelas and tuberculin. In 1917, he tried the inoculation of malaria parasites, which proved to be very successful in the case of dementia paralytica (also called general paresis of the insane), caused by neurosyphilis. This discovery earned him the Nobel Prize in Medicine in 1927. He died in 1940.

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David Wechsler

David Wechsler was an American psychologist who developed intelligence scales including the Wechsler Adult Intelligence Scale (WAIS) and the Wechsler Intelligence Scale for Children (WISC). He was born in 1896 in Lespezi, Romania. His family immigrated to the USA while he was a child. He earned his masters and PhD in psychology at Columbia University. During World War I, Wechsler, along with Charles Spearman (1863–1945) and Karl Pearson (1857–1936) created psychological tests designed to screen draftees. Wechsler eventually became chief psychologist at Bellevue Psychiatric Hospital in 1932, where he worked until his retirement in 1967. He died in 1981.

During his time at Bellevue, Wechsler first began developing intelligence tests. He disagreed with the single score of the 1937 Binet test. Instead, he emphasized that factors other than intellectual ability were involved in producing intelligent behavior. Wechsler believed that intelligence was made up of interdependent elements that could be defined, studied, and measured. He first produced the Wechsler Bellevue Intelligence Scale (WBIS) in 1939, which was the first intelligence test to incorporate a nonverbal performance scale. The WISC was published in 1949 as a revision of the WBIS specifically generated for children which measures verbal IQ, performance IQ, and full scale IQ. The WISC has also been used as a clinical tool to help in the diagnosis of ADHD and learning disabilities. The fifth edition of the test was recently released. The WAIS was a revision of the WBIS published in 1955 and designed for individuals 16 years of age or older, the fourth edition of which was published in 2008.

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Carl Wernicke

Carl Wernicke was a German anatomist and neuropathologist who is best known for identifying a sensory speech center in the temporal lobe. He was born in 1848 and received his medical degree from the University of Breslau. Wernicke then studied under the direction of Theodor Meynert and later served as an assistant to Karl Westphal in the psychiatry clinic at Charité Medical University of Berlin. Wernicke investigated the role of brain diseases on speech. He discovered that not all speech and language deficits were due to pathology of ventroposterior region of the frontal lobe (which had previously been identified by Paul Broca and is known as the Broca Area). Wernicke found that damage to the left posterior, superior temporal gyrus also produced impaired language comprehension and impaired ability to produce speech, a condition known as receptive (or Wernicke's) aphasia. This brain region is also popularly known as Wernicke's Area. Based on this and other findings, Wernicke proposed a hypothesis of a loosening of the continuity of the association fibers as the underlying mechanism for psychosis. Importantly, it proposed a neurological basis for psychiatric disorders. Wernicke became the Chair of neurology and psychiatry at the University of Breslau and later held a similar position at the University of Halle. He died in 1904.

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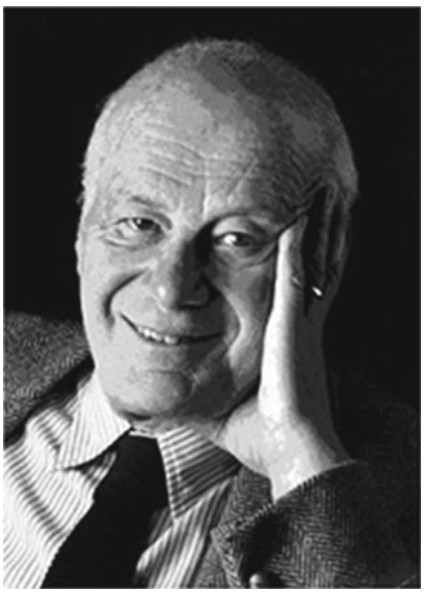
George Winokur



George Winokur was an American psychiatrist best known for his contributions to the fields of psychiatric genetics, affective disorders and for developing the Washington University criteria for "those adult psychiatric illnesses that have been sufficiently validated by precise clinical description, follow-up and family studies to warrant their use in research as well as in clinical practice." in association with Samuel Guze and Eli Robbins among others. The criteria are viewed as shifting away from psychodynamic theory to objective, criterion-based psychiatric diagnoses that helped provide a prototype for psychiatric diagnostic criteria that would later become enshrined in DSM-III, DSM-III-R, DSM-IV, and DSM-5. Winokur is also known for his use of molecular biology to investigate genetic linkage of known genetic markers with putative genes for affective disorders.

Winokur was born in 1925 in Philadelphia and received his medical degree from the University of Maryland in 1947. He worked at the Washington University School of Medicine for 20 years before being named the head of the Department of Psychiatry at the University of Iowa College of Medicine. Winokur served as department chair until he stepped down in 1990. Following his retirement in 1995, Winokur continued his research activities until his death in 1996.

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Wilhelm Wundt

Wilhelm Wundt was a German physician who is widely credited as being the father of experimental psychology. Wundt was born in 1832 in Neckarau. He received his medical degree from the University of Heidelberg in 1856. His early research was in the area of physiology and pathological anatomy. It was at the University of Heidelberg that he first taught a course in scientific psychology in which he stressed use of scientific methods to examine the physiological connection between the brain and mind. He published a collection of his lectures in 1864 as *Lectures on the Mind of Humans and Animals*. In 1874, he published the first, and one of the most important texts in psychology, *Principles of Physiological Psychiatry*. The principles described the use of self-examination of the conscious experience through observation to investigate feelings, emotions, volitions, and ideas. In 1875, Wundt began work at the University of Leipzig where he opened the first laboratory to be dedicated exclusively to measuring psychological phenomena. This represented the first time psychology was considered an independent field of study. Wundt was later Rector of Leipzig university from 1889 to 1890. He died in 1920.

Wundt believed the focus of psychology should be the scientific examination of an individual's experience of the mind. Wundt's method broke down an individual's consciousness to elemental sensations and feelings that could then analyzed, a technique described as Structuralism, and championed by one of his graduate students, Edward Titchener (1867–1927). Wundt analyzed these basic components through introspection, or the subjective observation of one's own experience. Wundt also influenced the field of psycholinguistics, noting that the mental sentence influences the verbal sentence and should be considered an element of speech.

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Huda Y. Zoghbi

Huda Zoghbi is a Lebanese-American neurologist and an expert on Rett syndrome. Zoghbi began her medical studies at the American University of Beirut, which were interrupted by the Lebanese Civil War. In 1975, she went to the USA and completed her studies at Meharry Medical College, receiving her M.D. in 1979. She then completed a residency in pediatric neurology at Baylor College of Medicine. She is currently a Professor in the Departments of Pediatrics—Neurology and Developmental Neuroscience, and Neuroscience; the Programs in Cell and Molecular Biology; Developmental Biology; and Translational Biology and Molecular Medicine at Baylor College of Medicine. She is also the Director of the Jan and Dan Duncan Neurological Research Institute at Texas Children's Hospital and an Investigator at the Howard Hughes Medical Research Institute.

It was during her residency that Zoghbi first came into contact with patients diagnosed with Rett syndrome. Through genetic experiments, Zoghbi and colleagues identified that mutations in the methyl CpG-binding protein 2 (MECP2) gene were responsible for causing Rett syndrome. Further studies have implicated MECP2 in autism and various forms of intellectual impairment. A series of animal experiments found that when MeCP2 was removed from GABAergic neurons in mice, most aspects of the Rett phenotype (i.e., lack of coordination, impaired social behavior, and presence of seizures) were reproduced. Research is currently underway to find ways of enhancing GABAergic signaling in Rett mouse models. Zoghbi has also identified the gene, mouse atonal homolog 1 (Math1) which is required for the production of numerous cell types including cerebellar granule cells, spinal cord neurons, and inner ear hair cells and is involved with balance and coordination.

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43
Normal Laboratory Values and Drug Therapeutic and Toxic Ranges

S. Hossein Fatemi, M.D, Ph.D., FACPsych

TABLE 43.1. Selected normal laboratory values used in psychiatry.

Test	Conventional units	SI units
Adrenocorticotropin (ACTH)[a]	6.0–76.0 pg/mL	1.3–16.7 pmol/L
Alanine aminotransferase (ALT, SGPT)[b]	7–41 U/L	0.12–0.70 µkat/L
Albumin[b]	3.3–4.9 g/dL	
Aldosterone[a,b]		
Supine, normal sodium diet	<16 ng/dL	<443 pmol/L
Upright, normal	4–31 ng/dL	111–858 pmol/L
Alkaline phosphatase[b]	33–96 U/L	0.56–1.63 µkat/L
Aluminum[b]	<5.41 µg/L	<0.2 µmol/L
Ammonia (NH_3)[a]	19–60 µg/dL	11–35 µmol/L
Amylase[b] (method dependent)	20–96 U/L	0.34–1.6 µkat/L
Androstenedione[b]		
Males	23–89 ng/dL	0.81–3.1 nmol/L
Females (premenopausal)	26–214 ng/dL	0.91–7.5 nmol/L
(postmenopausal)	13–82 ng/dL	0.46–2.9 nmol/L
Angiotensin-converting enzyme (ACE)[b]	9–67 U/L	0.15–1.1 µkat/L
Anion gap	7–16 mmol/L	7–16 mmol/L
Antidiuretic hormone (ADH) (Arginine vasopressin hormone)[a]	0–6.9 pg/mL with serum	
Anti-double-strand (native) DNA antibody[b]	<25 IU/L	<25 IU/L
Anti-mitochondrial antibody[b]	<20 units	Not applicable
Anti-neutrophil cytoplasmic autoantibodies[b]	<1:20	Not applicable
Antinuclear antibody (ANA)[b]	Negative at 1:40	Not applicable
Anti-Scl 70 antibody[b]	<1.0 U	Not applicable
Anti-Smith antibody[b]	<1.0 U	Not applicable
Anti-SSA antibody[b]	<1.0 U	Not applicable
Anti-SSB antibody[b]	Negative	Not applicable
Anti-thyroglobulin antibody[b]	<40 IU/mL	<40 KIU/L
Anti-thyroid peroxidase antibody[b]	<35 IU/mL	<35 KIU/L
Arsenic[c]	2–23 µg/L	0.03–0.31 µmol/L
Arterial blood gasses[c]		
$[HCO_3^-]$	22–30 meq/L	22–30 mmol/L
P_{CO2}	32–45 mmHg	4.3–6.0 kPa
pH	7.35–7.45	7.35–7.45
P_{O2}	72–104 mmHg	9.6–13.8 kPa
Aspartate aminotransferase (AST)[b]	12–38 U/L	0.20–0.65 µkat/L
Beta-2-microglobulin		
Serum	1.1–2.4 mg/L	1.1–2.4 mg/L
Urine	0–160 µg/L	0–160 µg/L

(continued)

S.H. Fatemi, M.D., Ph.D., FACPsych (✉)
Associate Chair for Neuroscience and Translational Research, Bernstein Endowed Chair in Adult Psychiatry, Professor, Departments of Psychiatry and Neuroscience, University of Minnesota School of Medicine, Minneapolis, MN, USA
e-mail: fatem002@umn.edu

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TABLE 43.1. (continued)

Test	Conventional units	SI units
Bilirubin[b]		
Total[b]	0.3–1.3 mg/dL	5.1–22 μmol/L
Direct	0.1–0.4 mg/dL	1.7–6.8 μmol/L
Indirect	0.2–0.9 mg/dL	3.4–15.2 μmol/L
Cadmium[c]	<5 μg/L	<44.5 nmol/L
Calcitonin[b]	Male: 0–7.5 pg/mL Female: 0–5.1 pg/mL	Male: 0–7.5 ng/L Female: 0–5.1 ng/L
Calcium		
Serum	8.7–10.2 mg/dL	2.2–2.6 mmol/L
Urine (on 200 mg/d dietary calcium)	Male: <300 mg/day Female: <250 mg/day	Male: <7.5 mmol/day Female: <6.2 mmol/day
Calcium, ionized[b]	4.5–5.3 mg/dL	1.12–1.32 mmol/L
Carbohydrate-deficient transferrin[b]	Male: <20 units Female: <26 units	Male: <27 units/L Female: <35 units/L
Carbon dioxide content (TCO_2)[b]	22–30 mEq/L	22–30 mmol/L
β-Carotene[b]	4–77 μg/dL	0.07–1.43 μmol/L
Ceruloplasmin[b]	25–43 mg/dL	250–430 mg/L
Cerebrospinal fluid (CSF)		
Osmolarity	292–297 mOsm/L	292–297 mmol/kg water
Electrolytes		
Sodium	137–145 mEq/L	137–145 mmol/L
Potassium	2.7–3.9 mEq/L	2.7–3.9 mmol/L
Calcium	2.1–3.0 mEq/L	1.0–1.5 mmol/L
Magnesium	2.0–2.5 mEq/L	1.0–1.2 mmol/L
Chloride	116–122 mEq/L	116–122 mmol/L
CO_2 content	20–24 mEq/L	20–24 mmol/L
P_{CO2}	45–49 mmHg	6–7 kPa
pH	7.31–7.34	7.31–7.34
Glucose	40–70 mg/dL	2.22–3.89 mmol/L
Lactate	10–20 mg/dL	1–2 mmol/L
Total protein		
Lumbar	15–50 mg/dL	0.15–0.5 g/L
Cisternal	15–25 mg/dL	0.15–0.25 g/L
Ventricular	6–15 mg/dL	0.06–0.15 g/L
Albumin	6.6–44.2 mg/dL	0.066–0.442 g/L
IgG	0.9–5.7 mg/dL	0.009–0.057 g/L
IgG index	–	0.29–0.59
Oligoclonal bands (OGB)	–	<2 bands not present in matched serum sample
Ammonia	25–80 μg/dL	15–47 μmol/L
CSF pressure	50–180 mmH_2O	–
CSF volume (adult)	–	~150 mL
Red blood cells	0	0
Leukocytes		
Total		0–5 mononuclear cells per μL
Differential		
Lymphocytes		60–70%
Monocytes		30–50%
Neutrophils		None
Chloride[b]	102–109 mEq/L	102–109 mmol/L
Cholesterol, total[b]		
Desirable	<200 mg/dL	
Borderline high	200–239 mg/dL	
High	≥ 240 mg/dL	
Complement[b] (adults)		
C3	83–177 mg/dL	0.83–1.77 g/L
C4	16–47 mg/dL	0.16–0.47 g/L
Total	60–144 CAE units	60–144 CAE units
Complete blood count (CBC)		
Hemoglobin (Hb)[c]	Male: 13.3–16.2 g/dL Female: 12.0–15.8 g/dL	Male: 133–162 g/L Female: 120–158 g/L
Hematocrit (Hct)[c]	Male: 38.8–46.4% Female: 35.4–44.4%	Male: 0.388–0.464 Female: 0.354–0.444
RBC count[c]	Male: $4.30–5.60 \times 10^6/mm^3$ Female: $4.0–5.20 \times 10^6/mm^3$	Male: $4.30–5.60 \times 10^{12}/L$ Female: $4.0–5.20 \times 10^{12}/L$

(continued)

TABLE 43.1. (continued)

Test	Conventional units	SI units
RBC indices[c]	Mean corpuscular volume: 79–93.3 μm^3 Mean corpuscular Hb: 26.7–31.9 pg/cell Mean corpuscular Hb concentration: 32.3–35.9 g/dL RBC distribution width: < 14.5%	Mean corpuscular volume: 79–93.3 fL Mean corpuscular Hb: 26.7–31.9 pg/cell Mean corpuscular Hb concentration: 323–359 g/L RBC distribution width: < 0.145
WBC count[c]	4.0–11.0 × $10^3/mm^3$	4.0–11.0 × 10^9/L
WBC differential[c]		
Relative counts	Neutrophils: 40–70% Bands: 0–5% Eosinophils: 0–6% Basophils: 0–2% Lymphocytes: 20–50% Monocytes: 4–8%	Neutrophils: 0.40–0.70 Bands: 0.0–0.05 Eosinophils: 0.0–0.06 Basophils: 0.0–0.02 Lymphocytes: 0.20–0.50 Monocytes: 0.04–0.08
Absolute counts	Neutrophils: 1,420–6,340/mm^3 Bands: 0–450/mm^3 Eosinophils: 0–540/mm^3 Basophils: 0–180/mm^3 Lymphocytes 710–4,530/mm^3 Monocytes 140–720/mm^3	Neutrophils: 1.42–6.34 × 10^9/L Bands: 0–0.45 × 10^9/L Eosinophils: 0–0.54 × 10^9/L Basophils: 0–0.18 × 10^9/L Lymphocytes 0.71–4.53 × 10^9/L Monocytes 0.14–0.72 × 10^9/L
Platelet count[c]	165–415 × $10^3/mm^3$	165–415 × 10^9/L
Mean platelet volume (MPV)	9.00–12.95	9.00–12.95 fL
Copper[b]	70–140 µg/dL	11–22 µmol/L
Cortisol, free[d]	24–108 µg/24 h	
Cortisol[b]		
Fasting, 8 am to noon	5–25 µg/dL	138–690 nmol/L
12 noon to 8 pm	5–15 µg/dL	138–414 nmol/L
8 pm to 8 am	0–10 µg/dL	0–276 nmol/L
C-Peptide[b] (insulin)	0.8–3.5 ng/mL	0.27–1.19 nmol/L
C-Reactive protein, high sensitivity	Cardiac risk Low: < 1.0 mg/L Average: 1.0–3.0 mg/L High: > 3.0 mg/L	Cardiac risk Low: < 1.0 mg/L Average: 1.0–3.0 mg/L High: > 3.0 mg/L
Creatine kinase (CK)		
Isoenzyme[b]		
CK–MB	Mass: 0.0–5.5 ng/mL Fraction of total activity (by electrophoresis): 0–4.0%	Mass: 0.0–5.5 µg/L Fraction of total activity (by electrophoresis): 0–0.04
Total:	Male: 51–294 U/L Female: 39–238 U/L	Male: 0.87–5.0 µkat/L Female: 0.66–4.00 µkat/L
Creatinine		
Serum	Male: 0.6–1.2 mg/dL Female: 0.5–0.9 mg/dL	Male: 53–106 µmol/L Female: 44–80 µmol/L
Urine	Male: 1–2 g/24 h Female: 0.8–1.8 g/24 h	
Cyanide[c]	< 0.1 mg/L	< 3.8 µmol/L
D-dimer[a]	220–740 ng/mL FEU	220–740 ng/mL FEU
Dopamine[a]	0–20 pg/mL	0–130 pmol/L
Epinephrine[a]		
Supine (30 min)	< 50 pg/mL	< 273 pmol/L
Sitting	< 60 pg/mL	< 328 pmol/L
Standing (30 min)	< 90 pg/mL	< 491 pmol/L
Erythrocyte sedimentation rate (ESR)[c]	Male: 0–15 mm/h Female: 0–20 mm/h	Male: 0–15 mm/h Female: 0–20 mm/h
Erythropoietin[b]	4–27 U/L	4–27 U/L
Estradiol[b]	Male: < 20 pg/mL Female: Follicular phase: < 20–145 pg/mL Mid-cycle peak phase: 112–443 pg/mL Luteal phase: < 20–241 pg/mL Postmenopausal: < 59 pg/mL	Male: 74 pmol/L Female: Follicular phase: 74–532 pmol/L Mid-cycle peak phase: 411–1,626 pmol /L Luteal phase: 74–885 pmol/L Postmenopausal: 217 pmol/L
Estrone[b]	Male: 9–36 pg/mL Female: Follicular phase: < 150 pg/mL Luteal phase: < 200 pg/mL Postmenopausal: 3–32 pg/mL	Male: 33–133 pmol/L Female: Follicular phase: < 555 pmol/L Luteal phase: < 740 pmol/L Postmenopausal: 11–118 pmol/L

(continued)

TABLE 43.1. (continued)

Test	Conventional units	SI units
Ferritin[b]	Male: 29–248 ng/mL Female: 10–150 ng/mL	Male: 29–248 µg/L Female: 10–150 µg/L
Folic acid		
RBC	150–450 ng/mL cells	340–1,020 nmol/L cells
Serum	5.4–18.0 ng/mL	12.2–40.8 nmol/L
Follicle-stimulating hormone (FSH)[b]	Male: 1–12 mIU/mL Female: Follicular phase: 3–20 mIU/mL Ovulatory phase: 9–26 mIU/mL Luteal phase: 1–12 mIU/mL Postmenopausal: 18–153 mIU/mL	Male: 1–12 IU/L Female: Follicular phase: 3–20 IU/L Ovulatory phase: 9–26 IU/L Luteal phase: 1–12 IU/L Postmenopausal: 18–153 IU/L
γ-Glutamyltransferase (GGT)[b]	9–58 U/L	0.15–0.99 µkat/L
Gastrin[b]	0–200 pg/mL	0–200 µg/L
Glomerular filtration rate	>60 mL/min/1.73 m^2 For African Americans, multiply the result by 1.21	>60 mL/min/1.73 m^2 For African Americans, multiply the result by 1.21
Glucagon[a]	40–130 pg/mL	40–130 ng/L
Glucose[c]	65–95 mg/dL	3.6–5.3 mmol/L
Glucose (fasting)[a]		
Normal	75–100 mg/dL	4.2–5.6 mmol/L
Increased risk for diabetes	100–125 mg/dL	5.6–6.9 mmol/L
Diabetes mellitus[b]	Fasting: >126 mg/dL A 2-h level of ≥200 mg/dL during an oral glucose tolerance test A random glucose level of ≥200 mg/dL in patients with symptoms of hyperglycemia	Fasting: >7.0 mmol/L A 2-h level of ≥11.1 mmol/L during an oral glucose tolerance test A random glucose level of ≥11.1 mmol/L in patients with symptoms of hyperglycemia
Glucose-6-phosphate dehydrogenase (G6PD)[c]	7–20.5 U/g Hb	7–20.5 U/g Hb
Growth hormone (GH)[b] (resting)	0–5 ng/mL	0–5 µg/L
Hematocrit (Hct)[c]	Male: 38.8–46.4% Female: 35.4–44.4%	Male: 0.388–0.464 Female: 0.354–0.444
Hemoglobin (Hb)[c]		
Plasma	0.6–5.0 mg/dL	6–50 mg/L
Whole blood	Male: 13.3–16.2 g/dL Female: 12.0–15.8 g/dL	Male: 133–162 g/L Female: 120–158 g/L
A_{1c}	4.0–5.6%	0.04–0.06 Hb fraction
Prediabetes	5.7–6.4%	0.057–0.064 Hb fraction
Diabetes mellitus	A hemoglobin A_{1c} level of ≥6.5% as suggested by the American Diabetes Association	A hemoglobin A_{1c} level of ≥0.065 Hb fraction as suggested by the American Diabetes Association
High-density lipoprotein (HDL)[b]		
Low	<40 mg/dL	
High	≥ 60 mg/dL	
Homocysteine[a]	4.4–10.8 µmol/L	4.4–10.8 µmol/L
Human chorionic gonadotropin (hCG)		
Female		
Nonpregnant	<5 mIU/mL	<5 IU/L
Pregnancy:		
1–2 weeks postconception	9–130 mIU/mL	9–130 IU/L
2–3 weeks postconception	75–2,600 mIU/mL	75–2,600 IU/L
3–4 weeks postconception	850–20,800 mIU/mL	850–20,800 IU/L
4–5 weeks postconception	4,000–100,200 mIU/mL	4,000–100,200 IU/L
5–10 weeks postconception	11,500–289,000 mIU/mL	11,500–289,000 IU/L
10–14 weeks postconception	18,300–137,000 mIU/mL	18,300–137,000 IU/L
Second trimester	1,400–53,000 mIU/mL	1,400–53,000 IU/L
Third trimester	940–60,000 mIU/mL	940–60,000 IU/L
17-Hydroxycorticosteroids[d]	Male: 6–16 mg/24 h Female: 4–8 mg/24 h	
5-Hydroxyindoleacetic acid (5-HIAA)[d]	0–15 mg/24 h	0–78.8 µmol/24 h
17-Hydroxyprogesterone (adult)[b]		
Male	<139 ng/dL	<4.17 nmol/L
Female		
Follicular phase	15–70 ng/dL	0.45–2.1 nmol/L
Luteal phase	35–290 ng/dL	1.05–8.7 nmol/L

(continued)

TABLE 43.1. (continued)

Test	Conventional units	SI units
Immunoglobulin[b]		
IgA	70–350 mg/dL	0.7–3.50 g/L
IgD	0–14 mg/dL	0–140 mg/L
IgE	1–87 IU/mL	1–87 KIU/L
IgG (total)	700–1,700 mg/dL	7–17 g/L
IgG_1	270–1,740 mg/dL	2.7–17.4 g/L
IgG_2	30–630 mg/dL	0.3–6.3 g/L
IgG_3	13–320 mg/dL	0.13–3.2 g/L
IgG_4	11–620 mg/dL	0.11–6.2 g/L
IgM	50–300 mg/dL	0.50–3.0 g/L
Insulin[a,b]	2–20 μU/mL	14.35–143.5 pmol/L
Iron[b]	41–141 μg/dL	7–25 μmol/L
Iron-binding capacity[b]	251–406 μg/dL % Saturation: 16–35%	45–73 μmol/L % Saturation: 0.16–0.35%
Lactate dehydrogenase (LD)[b]	115–221 U/L	2.0–3.8 μkat/L
Lactic acid[a]		
Venous	4.5–19.8 mg/dL	0.5–2.2 mmol/L
Arterial	4.5–14.4 mg/dL	0.5–1.6 mmol/L
Lead[b] (adult)	< 10 μg/dL	< 0.5 μmol/L
Lipase[b]	3–43 U/L	0.51–0.73 μkat/L
Lipoprotein (a)[b]	0–30 mg/dL	0–300 mg/L
Low-density lipoprotein (LDL) cholesterol, direct[b]		
Desirable, for high-risk patients	< 70 mg/dL	
Optimal	< 100 mg/dL	
Near optimal/above optimal	100–129 mg/dL	
Borderline high	130–159 mg/dL	
High	160–189 mg/dL	
Very high	≥ 190 mg/dL	
Luteinizing hormone (LH)[b]		
Male	2–12 mIU/mL	2–12 U/L
Female		
Follicular phase	2–15 mIU/mL	2–15 U/L
Ovulatory phase	22–105 mIU/mL	22–105 U/L
Luteal phase	0.6–19.0 mIU/mL	0.6–19.0 U/L
Pregnancy	< 1.04 mIU/mL	< 1.04 U/L
Postmenopausal	16–64 mIU/mL	16–64 U/L
Lymphocyte surface markers (T cell)[c]		
CD4	Absolute: 640–1,175 cells/μL Percentage: 40–62%	Absolute: $0.64–1.18 \times 10^9$ cells/L Percentage: 40–62%
CD8	Absolute: 335–875 cells/μL Percentage: 20–36%	Absolute: $0.34–0.88 \times 10^9$ cells/L Percentage: 20–36%
Helper/suppressor (CD4/CD8) ratio	1–4	1–4
Magnesium[b]	1.5–2.3 mg/dL	0.62–0.95 mmol/L
Mercury		
Urine	< 20 μg/L	< 99.8 nmol/L
Blood	0.6–59 μg/L	3.0–294 nmol/L
Metanephrine[a]	< 100 pg/mL	< 0.5 nmol/L
Methemoglobin[c]	0–1% of total Hb	0–0.01 of total Hb
Microalbumin[d]		
Normal	0–30 mg/24 h	0.0–0.03 g/24 h
Microalbuminuria	30–300 mg/24 h	0.03–0.30 g/24 h
Clinical albuminuria	> 300 mg/24 h	> 0.3 g/24 h
Myelin basic protein[e]	< 4 ng/mL	< 4 μg/L
Myoglobin[b]	Male: 20–71 μg/L Female: 25–58 μg/L	Male: 20–71 μg/L Female: 25–58 μg/L
Nitrogen, total[f]	< 2.5 g/24 h	< 178 mmol/24 h
Norepinephrine		
Supine (30 min)	110–410 pg/mL	650–2,423 pmol/L
Sitting	120–680 pg/mL	709–4,019 pmol/L
Standing (30 min)	125–700 pg/mL	739–4,137 pmol/L
5' Nucleotidase	0–11 U/L	0.00–0.19 μkat/L

(continued)

TABLE 43.1. (continued)

Test	Conventional units	SI units
Osmolality		
Plasma	275–295 mOsmol/kg serum water	275–295 mOsmol/kg serum water
Urine	500–800 mOsmol/kg water	500–800 mOsmol/kg water
Oxalate[d]		
Male	7–44 mg/24 h	80–500 µmol/24 h
Female	4–31 mg/24 h	45–350 µmol/24 h
Oxygen saturation (sea level)	Percent:	Fraction:
Arterial	94–100%	0.94–1.0
Venous, arm	60–85%	0.60–0.85
Parathyroid hormone (PTH)[b] intact	8–51 pg/mL	8–51 ng/L
Partial thromboplastin time (PTT) activated[a]	26.3–39.4 sec	26.3–39.4 sec
Phosphorus, inorganic[b]	2.5–4.3 mg/dL	0.81–1.4 mmol/L
Platelet count[c]	$165–415 \times 10^3/mm^3$	$165–415 \times 10^9/L$
Porphobilinogen[d]	None	None
Potassium[b]	3.5–5.0 meq/L	3.5–5.0 mmol/L
Prealbumin[b]	17–34 mg/dL	170–340 mg/L
Progesterone[b]	Male: <1.0 ng/mL Female: Follicular phase: <1.0 ng/mL Midluteal phase: 3–20 ng/mL	Male: <3.18 nmol/L Female: Follicular phase: <3.18 nmol/L Luteal phase: 9.54–63.6 nmol/L
Prolactin[b]	Male: 2.5–17 ng/mL Female: Nonpregnant: 1.9–25 ng/mL	Male: 53–360 mIU/L Female: Nonpregnant: 40–530 mIU/L
Prostate-specific antigen (PSA)[b] (male)	0.0–4.0 ng/mL	0.0–4.0 µg/L
Protein, total[d]	<150 mg/24 h	<0.15 g/24 h
Protein fractions[b]		
Albumin	3.5–5.5 g/dL (50–60%)	35–55 g/L
Globulin	2.0–3.5 g/dL (40–50%)	20–35 g/L
α_1	0.2–0.4 g/dL (4.2–7.2%)	2–4 g/L
α_2	0.5–0.9 g/dL (6.8–12%)	5–9 g/L
β	0.6–1.1 g/dL (9.3–15%)	6–11 g/L
γ	0.7–1.7 g/dL (13–23%)	7–17 g/L
Prothrombin time (PT)[a]	12.7–15.4 sec	12.7–15.4 sec
Protoporphyrin[c]		
Free erythrocyte	16–36 µg/dL RBCs	0.28–0.64 µmol/L RBCs
Zinc	<70 µg/dL	<700 µg/L
Pyruvate[a]	0.35–1.14 mg/dL	40–130 µmol/L
Reticulocyte count[c]	Males: 0.8–2.3% RBCs Females: 0.8–2.0% RBCs	Males: 0.008–0.023 RBCs Females: 0.008–0.020 RBCs
Rheumatoid factor[b]	<15 IU/mL	<15 kIU/L
Selenium[b]	63–160 µg/L	0.8–2.0 µmol/L
Serotonin[c]	50–200 ng/mL	0.28–1.14 µmol/L
Platelets	125–500 ng/10^9 platelets	0.7–2.8 amol/platelet
Sodium[b]	136–146 mEq/L	136–146 mmol/L
Somatomedin-C (IGF-1) (adult)[b]		
16 years	226–903 ng/mL	226–903 µg/L
21–25 years	116–358 ng/mL	116–358 µg/L
36–40 years	119–204 ng/mL	119–204 µg/L
66–70 years	69–200 ng/mL	69–200 µg/L
81–85 years	55–166 ng/mL	55–166 µg/L
Somatostatin[a]	<25 pg/mL	<25 ng/L
T_3 (triiodothyronine)[b]		
Free	2.4–4.2 pg/mL	3.7–6.5 pmol/L
Total	77–135 ng/dL	1.2–2.1 nmol/L
T_4 (thyroxine)[b]		
Free	0.7–1.24 ng/dL	9.0–16 pmol/L
Total	5.4–11.7 µg/dL	70–151 nmol/L
Testosterone, free[b]		
Male	90–300 pg/mL	312–1,041 pmol/L
Female	3–19 pg/mL	10.4–65.9 pmol/L
Testosterone, total[b] (morning sample)		
Male	270–1,070 ng/dL	9.36–37.10 nmol/L
Female	6–86 ng/dL	0.21–2.98 nmol/L
Thrombin time[a]	15.3–18.5 sec	15.3–18.5 sec

(continued)

TABLE 43.1. (continued)

Test	Conventional units	SI units
Thyroglobulin[b]	1.3–31.8 ng/mL	1.3–31.8 µg/L
Thyroid-binding globulin[b]	1.3–3.0 mg/dL	13–30 mg/L
Thyroid-stimulating hormone (TSH)[b]	0.34–4.25 µIU/mL	0.34–4.25 mIU/L
Thyroxine index (free)	6.7–10.9	6.7–10.9
Transferrin[b]	200–400 mg/dL	2–4 g/L
Triglycerides[b]	<150 mg/dL	<1.7 mmol/L
Troponin I[b] (method dependent) 99th percentile of a healthy population	0–0.04 ng/mL	0–0.04 µg/L
Troponin T[b] 99th percentile of a healthy population	0–0.01 ng/mL	0–0.01 µg/L
Urea nitrogen		
Blood (BUN)[b]	7–20 mg/dL	2.5–7.1 mmol/L
Urine	6–17 g/d	214–607 mmol/d
Uric acid		
Serum	Male: 3.1–7.0 mg/dL Female: 2.5–5.6 mg/dL	Male: 0.18–0.41 mmol/L Female: 0.15–0.33 mmol/L
Urine (normal diet)	250–800 mg/24 h	1.49–4.76 mmol/24 h
Urinalysis, complete[d]		
Appearance	clear, yellow	
Specific gravity		
Normal	1.003–1.030	1.003–1.030
After 12-h fluid restriction	>1.025	>1.025
After 12-h deliberate water Intake	≤1.003	≤1.003
pH	5.0–9.0	
Bacteria	None	
Crystals	Negative	
Protein	Negative	
Glucose	Negative	
Hyaline casts	0–5/low-power field	
Reducing substances	Negative	
Ketones	Negative	
Bilirubin	Negative	
Occult blood	Negative	
WBC esterase	Negative	
Nitrite	Negative	
WBC	0–2/high-power field	
RBC	0–2/high-power field	
Renal epithelial cells	≤3/high-power field	
Squamous epithelial cells	None or few/high-power field	
Yeast	None	
Vanillylmandelic acid (VMA)[d]	<6 mg/24 h	<30 µmol/24 h
Vasoactive intestinal polypeptide (VIP)[a]	0–60 pg/mL	0–60 ng/L
Vitamin A[b]	20–100 µg/dL	0.7–3.5 µmol/L
Vitamin B_1 (thiamine)[b]	0–2 µg/dL	0–75 nmol/L
Vitamin B_2 (riboflavin)[b]	4–24 µg/dL	106–638 nmol/L
Vitamin B_6[a]	5–30 ng/mL	20–121 nmol/L
Vitamin B_{12}[b]	279–996 pg/mL	206–735 pmol/L
Vitamin C[b]	0.4–1.0 mg/dL	23–57 µmol/L
1,25-Dihydroxyvitamin D_3[a,b], total	15–75 pg/mL	36–180 pmol/L
25-Hydroxyvitamin D_3[a], total	30–100 ng/mL	75–250 nmol/L
Vitamin E[b]	5–18 µg/mL	12–42 µmol/L
Vitamin K[b]	0.13–1.19 ng/mL	0.29–2.64 nmol/L
Coenzyme Q_{10} (ubiquinone)[a]	433–1,532 µg/L	433–1,532 µg/L
Zinc[b]	75–120 µg/dL	11.5–18.4 µmol/L
Zinc protoporphyrin[c]	0–40 µg/dL	0–400 µg/L

[a]Plasma, [b]serum, [c]blood, [d]urine, [e]CSF, [f]feces.

µkat microkatal, *L* liter (1,000 mL), *U* unit, *g* gram, *dL* deciliter (100 mL), *nmol* 10^{-9} mol, *pg* picogram or 10^{-12} of a gram, *mOsm* milliosmolal, *KU* kilounit, *amol* attomol or 10^{-18} mol.

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Because of the potential variability between laboratory values presented here and local values, we highly recommend that the reader check reference levels from this table against local laboratory reference ranges.

TABLE 43.2. Therapeutic range and toxicity of selected drugs.

Drug	Therapeutic range Conventional Units	Alert level[a]	Toxic range Conventional Units
Acamprosate[b]	250–700 ng/mL	1,000 ng/mL	
Acetaminophen[b]	10–30 µg/mL		>200 µg/mL
Agomelatine[b]	7–300 ng/mL 1–2 h after 50 mg	600 ng/mL	
Alprazolam[b]	5–50 ng/mL	100 ng/mL	
Amantadine[b]	300–600 ng/mL	1,200 ng/mL	
Amitriptyline and its metabolite, nortriptyline, total[b]	80–200 ng/mL	300 ng/mL	>500 ng/mL
Amobarbital[b]	1–5 µg/mL		>10 µg/mL
Amphetamine[b]	20–30 ng/mL		>200 ng/mL
Aripiprazole[b]	150–500 ng/mL	1,000 ng/mL	
Asenapine[b]	2–5 ng/mL	10 ng/mL	
Atomoxetine[b]	200–1,000 ng/mL 60–90 min after intake of 1.2 mg/kg/day	2,000 ng/mL	
Barbiturates, most short acting[b]			>35 mg/L
Biperiden[b]	Cmax 1–6.5 ng/mL 0.5–2 h after 4 mg	13 ng/mL	
Buprenorphine[b]	0.7–1.6 ng/mL Cmax: <9 ng/mL after 24 mg	10 ng/mL (Cmax)	
Bupropion and hydroxybupropion[b]	50–100 ng/mL 550–1,500 ng/mL	 2,000 ng/mL	300 ng/mL n.d.
Buspirone[b]	1–4 ng/mL	8 ng/mL	n.d.
Carbamazepine[b]	4–10 µg/mL	20 µg/mL	
Chlordiazepoxide and metabolite, desmethyl chlordiazepoxide total[b]	400–3,000 ng/mL	3,500 ng/mL	
Chlorpromazine[b]	30–300 ng/mL	600 ng/mL	>750 ng/mL
Citalopram[b]	50–110 ng/mL	220 ng/mL	
Clomipramine plus Norclomipramine	230–450 ng/mL	450 ng/mL	
Clonazepam[b]	20–70 ng/mL	80 ng/mL	
Clorazepate[b]	0.12–2.2 µg/mL		>5,000 ng/mL
Clozapine	350–600 ng/mL	1,000 ng/mL	
Cocaine			>1,000 ng/mL
Desipramine[b]	100–300 ng/mL	300 ng/mL	
Desvenlafaxine[b]	100–400 ng/mL	600 ng/mL	
Dexmethylphenidate[b]	13–23 ng/mL 4 h after 20 mg	44 ng/mL	
Diazepam and its metabolites	200–2,500 ng/mL	3,000 ng/mL	
Digoxin[b]	0.5–2.0 ng/mL	>2.5 ng/mL	>3.9 ng/mL
Disulfiram[b]	50–400 ng/mL	500 ng/mL	
Donepezil[b]	30–75 ng/mL	75 ng/mL	
Doxepin plus Nordoxepin	50–150 ng/mL	300 ng/mL	
Duloxetine[b]	30–120 ng/mL	240 ng/mL	
Escitalopram[b]	15–80 ng/mL	160 ng/mL	
Ethanol – Behavioral changes – Intoxication	 >20 mg/dL >100 mg/dL		
Fluoxetine and its metabolite norfluoxetine, total[b]	120–500 ng/mL	1,000 ng/mL	
Fluphenazine[b]	1–10 ng/mL	15 ng/mL	
Fluvoxamine[b]	60–230 ng/mL	500 ng/mL	
Gabapentin[b]	2–20 µg/mL	25 µg/mL	
Galantamine[b]	30–60 ng/mL	90 ng/mL	
Haloperidol[b]	1–10 ng/mL	15 ng/mL	
Ibuprofen[b]	10–50 µg/mL		100–700 ng/mL
Iloperidone	5–10 ng/mL	20 ng/mL	
Imipramine and its metabolite desipramine, total[b]	175–300 ng/mL	300 ng/mL	
Lamotrigine	3–14 µg/mL	30 µg/mL	
Levomethadone[b]	250–400 ng/mL	400 ng/mL or 100 ng/mL in nonusers of opiates	
Levomilnacipran	40 mg, Cmax 59.7 ng/mL 120 mg, Cmax 341 ng/mL		

(continued)

TABLE 43.2. (continued)

Drug	Therapeutic range Conventional Units	Alert level[a]	Toxic range Conventional Units
Lithium[b] • Acute mania • Polyuria, blurred vision, lethargy, increased reflexes, fasiculations • Myoclonus, incontinence, stupor, restlessness, coma • Seizures, Hypotension and arrhythmias, • Coma, death	0.6–1.2 mEq/L 0.8–1.0 mEq/L		 1.5–2.25 mEq/L 2.5–3.0 mEq/L >3.0 mEq/L >4.0 mEq/L
Lorazepam[b]	10–15 ng/mL	30 ng/mL	
Maprotiline[b]	75–130 ng/mL	220 ng/mL	
Melperone	30–100 ng/mL	200 ng/mL	
Memantine[b]	90–150 ng/mL	300 ng/mL	
Meprobamate[b]	6–12 µg/mL		>60 µg/mL
Methadone[b]	400–600 ng/mL	600 ng/mL or 300 ng/mL in non-opiate users	
Methotrexate[b] – Low dose (1–2 weeks) – High dose (48 h)	variable		 >9.2 ng/mL >227 ng/mL
Methylphenidate[b]	13–22 ng/mL d-methylphenidate 2 h after 20 mg immediate release or 6–8 h after 40 mg extended release	44 ng/mL	
Mianserine[b]	15–70 ng/mL	140 ng/mL	
Midazolam[b]	6–15 ng/mL Cmax: 60–80 ng/mL	1,000 ng/mL	
Milnacipran[b]	50–110 ng/mL	220 ng/mL	
Mirtazapine[b]	30–80 ng/mL	160 ng/mL	
Moclobemide[b]	300–1,000 ng/mL	2,000 ng/mL	
Modafinil[b]	1,000–1,700 ng/mL after 200 mg/day	3,400 ng/mL	
Molindone[b]	30–70 ng/mL		≥200 ng/mL
Morphine[b]	10–80 ng/mL		
Naltrexone plus 6β-naltrexol[b]	25–100 ng/mL	200 ng/mL	
Nortriptyline[b]	70–170 ng/mL	300 ng/mL	
Olanzapine	20–80 ng/mL	150 ng/mL	
Oxazepam[b]	200–1,500 ng/mL	2,000 ng/mL	
Oxcarbazepine plus 10-hydroxycarbazepine[b]	10–35 µg/mL	40 µg/mL	
Paliperidone[b]	20–60 ng/mL	120 ng/mL	
Paroxetine	30–120 ng/mL	240 ng/mL	
Pentobarbital[b]	1–5 µg/mL		>50 µg/mL
Perphenazine	0.6–2.4 ng/mL	5 ng/mL	
Phenobarbital[b] • Slowness, ataxia, nystagmus • Coma with reflexes • Coma without reflexes	15–40 µg/mL	50 µg/mL	 35–80 µg/mL 65–117 µg/mL >100 µg/mL
Phenytoin[b]	10–20 µg/mL	25 µg/mL	
Pimozide	15–20 ng/mL	20 ng/mL	
Pipamperone	100–400 ng/mL	500 ng/mL	
Pramipexole	0.39–7.17 ng/mL	15 ng/mL	
Pregabalin	2–5 µg/mL	10 µg/mL	
Propranolol[b]	50–100 ng/mL		>1,000 ng/mL
Quetiapine[b]	100–500 ng/mL	1,000 ng/mL	
Reboxetine	60–350 ng/mL	700 ng/mL	
Risperidone plus 9-hydroxyrisperidone[b]	20–60 ng/mL	120 ng/mL	
Rivastigmine[b]	Oral 8–20 ng/mL (1–2 h after dose) Patch 5–13 ng/mL (1 h before application of a new patch)	40 ng/mL	
Salicylate[b]	15–30 mg/dL		>30 mg/dL
Sertraline[b]	10–150 ng/mL	300 ng/mL	
Temazepam[b]	20–900 ng/mL	1,000 ng/mL	
Theophylline[b]	8–20 µg/mL		>25 µg/mL

(continued)

TABLE 43.2. (continued)

Drug	Therapeutic range Conventional Units	Alert level[a]	Toxic range Conventional Units
Thioridazine	100–200 ng/mL	400 ng/mL	
Thiothixene	2–15 ng/mL		
Topiramate[b]	2–8 µg/mL (morning levels)	16 µg/mL	
Tranylcypromin[b]	≤50 ng/mL	100 ng/mL	
Trazodone[b]	700–1,000 ng/mL	1,200 ng/mL	
Triazolam[b]	2–20 ng/mL	40 ng/mL	
Trifluoperazine	4–40 ng/mL		>50 ng/mL
Trimipramine	150–300 ng/mL	600 ng/mL	
Valproic acid[b]	50–100 µg/mL	120 µg/mL	
Venlafaxine and o-desmethylvenlafaxine[b]	100–400 ng/mL	800 ng/mL	
Verapamil[b]	100–250 ng/mL		>250 ng/mL
Varenicline[b]	4–5 ng/mL	10 ng/mL	
Ziprasidone[b]	50–200 ng/mL	400 ng/mL	
Zolpidem[b]	80–150 ng/mL	300 ng/mL	
Zopiclone[b]	10–50 ng/mL	150 ng/mL	

[a]Alert level indicates an arbitrarily defined plasma concentration twofold higher than the upper limit of the therapeutic reference range (for more details, please see Hiemke et al., 2011), [b]serum.

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Because of the potential variability of serum levels of various drugs measured by different laboratories, we highly recommend that the reader should check levels of drugs from this table against local laboratory values. As state of knowledge changes, some of the drug levels may change. Please see Chap. 31 for differences in values for several drugs, e.g., amitriptyline, bupropion, citalopram, desipramine, fluoxetine, fluvoxamine, olanzapine, sertraline, and venlafaxine.

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