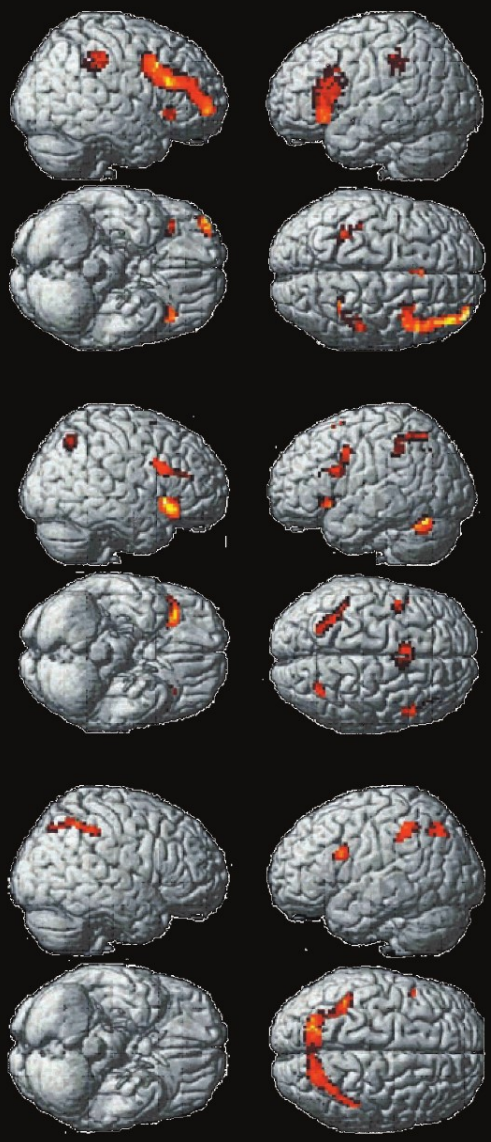
Edited by

S. Hossein Fatemi, MD, PhD

Paula J. Clayton, MD

The Medical Basis of Psychiatry

Third Edition



Humana Press

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Foreword by

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Cover illustration: *see* Fig. 38.2 and discussion on p. 708.

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To George Winokur.

SHF and PJC

To my father, S. Mehdi Fatemi, and to my family, S. Ali Fatemi, MD, Naheed Fatemi, Parvin Fatemi, S. Mohammad Fatemi, Neelufaar Fatemi, Maryam Jalali-Mousavi, and last but not least, my mother, Fatemeh Parsa Moghaddam, whose love and support have enabled me to complete this work.

SHF

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.

PJC

Foreword

This book has brought together the contributions of more than 70 outstanding experts in their fields, and this alone should be enough to recommend it to psychiatrists and others engaged in mental health research and education, as well as to those focusing on the organization and provision of mental health care. But there are other features in this assembly of excellent chapters that speak for this volume and make it quite unique.

Thus, the editors of *The Medical Basis of Psychiatry*, Third Edition, have demonstrated that several important issues often presented as major dilemmas before psychiatrists are in fact minor problems, and, therefore, discussion about them should not be allowed to block progress. The first is deciding between a classification of mental disorders in groups of categories versus a crosswise examination of the domain of psychiatry by means of dimensions of functioning. Both are possible and necessary, and the series of chapters dealing with groups of categories of mental disorders that opens this book is richly complemented by the chapters that deal with dimensions of functioning, such as thought disorder and disturbances of mood. Another dilemma is the biological versus nonbiological approach to psychiatric problems: here again, the chapters on various methods of investigation, i.e., in the laboratory, in the application of neuroimaging techniques, and in epidemiological studies, clearly show the advantages of each of these approaches without diminishing the value of the others. The dilemma of biological versus nonbiological treatments is also resolved in a similar manner, showing even more clearly that the editors took a balanced, ecumenical, and practical approach to the key aspects of today's psychiatry.

It gives me great pleasure, therefore, to thank the editors of and contributors to *The Medical Basis of Psychiatry*, Third Edition, for their efforts, which have resulted in such a comprehensive review of current evidence and issues of relevance to psychiatry, and to express the hope that this work will find the wide distribution that its quality and coverage richly deserves.

Norman Sartorius, MD, PhD
Geneva, Switzerland

Preface

Nearly 14 years have elapsed since the second edition of this book was published. George Winokur pioneered the early editions of this book and contributed significantly to the scientific value of this book by recruiting first-class psychiatrists and neuroscientists to contribute. However, George Winokur's major contribution to the advancement of psychiatry remains his development of the Washington University criteria, along with Samuel Guze, Eli Robins, John Feighner, Robert Woodruff Jr., and Rodrigo Munoz. These criteria revolutionized and promulgated the first scientific classification of psychiatric nosology. Psychiatry has emerged as a burgeoning scientific field with major advances in etiology and treatment of several disorders. Just as there was excitement in the anatomic advances that took place a hundred years ago when Emil Kraepelin and his collaborators took on the enormous task of classifying psychiatric disorders based on rational scientific thinking, new advances in genetics, biochemistry, neuroanatomy, and pharmacotherapy of mental disorders have brought us even closer to a better understanding of complex disorders such as schizophrenia, bipolar disorder, depression, and even autism.

The major goal of previous editions of *The Medical Basis of Psychiatry* was to update the busy clinician, psychiatric resident, and medical student with the most current information on the etiology, diagnosis, and treatment of psychiatric disorders. This goal has been our focus for the third edition. All attempts have been made to provide the reader with the most up-to-date information and literature supported by a close survey of the field. We are grateful to all the chapter authors, who have strived to provide the reader with the biological foundations of psychiatry. The Third Edition adds chapters dealing with new concepts in biology and treatment of mental disorders. We are optimistic that *The Medical Basis of Psychiatry*, Third Edition, upholds the standards of this classic textbook, and that its focus on the biologic and medical aspects of psychiatry will continue to be of significant help to all interested in the scientific practice of psychiatry.

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Many have helped to make the publication of this book possible, including Dr. John Vuchetich. We are especially indebted to Mr. Timothy D. Folsom, who faithfully reviewed all chapters for accuracy and worked as a liaison between the editors and the authors of the chapters and Ms. Teri Jane Reutiman, for help with various aspects of editing this book. We are grateful to Ms. Laurie Iversen for clerical assistance. We are also grateful to Dr. Alessandro Guidotti and Dr. Shitij Kapur for their contributions to Chapter 40.

We are also grateful to the publishers and authors who have generously given approval for reproduction of tables and figures, as well as to Mr. Richard Lansing, Mr. John Morgan, Ms. Sharmila Krishnamurthy, of Integra, and the Humana Press for an excellent job in publishing this book.

SHF
PJC

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Color Plates

Color plates follow p. 650.

COLOR PLATE 1 **a** Several Reelin-positive cells are localized to the hilus (CA4) of hippocampal complex. *M*, dentate inner molecular layer, *GC*, granular cell layer. Original magnification, × 40. **b** 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 subject (**C**). (**a** Reprinted with permission from the Nature Publishing Group (47). **b** Reprinted with permission from Lippincott Williams and Wilkins (178)) (Fig. 6.2; *see* complete caption and discussion on p. 89).

COLOR PLATE 2 Ventricular size in monozygotic twins discordant for schizophrenia. Coronal MRI scans of twins discordant for schizophrenia show lateral ventricular enlargement in the affected twin (reprinted with permission from the Massachusetts Medical Society (179). All rights reserved) (Fig. 6.3; *see* discussion on p. 90).

COLOR PLATE 3 These camera lucida drawings compare the distribution of nicotinamide–adenine dinucleotide phosphate–diaphorase-positive-stained neurons (*squares*) in sections through the superior frontal gyrus of a control and schizophrenic brain. There is a significant shift in the direction of the diaphorase positive neurons in the white matter in the schizophrenic brain. Numbers 1 to 8 indicate compartments of the brain; Roman numerals indicate the cortical layers (reprinted with permission from the American Medical Association (60). All rights reserved) (Fig. 6.4; *see* discussion on p. 90).

COLOR PLATE 4 Reduction of fractional anisotropy (*FA*) in the posterior hippocampus in children and adolescents with schizophrenia compared with control subjects. 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 (courtesy of the Youth Psychosis Research Group at the University of Minnesota; further information is described in reference (21)) (Fig. 22.1; *see* discussion on p. 393).

COLOR PLATE 5 Temporal lobotomy (Fig. 26.1; *see* discussion on p. 447).

COLOR PLATE 6 Normal SPECT scan (Fig. 26.2; *see* discussion on p. 447).

COLOR PLATE 7 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 healthy control subjects for developing the disorders listed above (Fig. 29.1; *see* discussion on p. 492).

COLOR PLATE 8 P50 abnormality in schizophrenia. (Fig. 29.2; *see* complete caption on p. 506 and discussion on p. 505).

COLOR PLATE 9 A 30-second epoch of REM sleep is exemplified by rapid eye movements (*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*) (Fig. 37.2; *see* discussion on p. 663).

COLOR PLATE 10 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 Elsevier, Inc (Fig. 37.3; *see* discussion on p. 664).

COLOR PLATE 11 A 30-second epoch demonstrating an abrupt arousal from non-REM stages 3/4 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 classic sleep terrors (Fig. 37.6; *see* discussion on p. 680).

COLOR PLATE 12 The appearance of partial volume effects in PET images. Grey matter is fourfold as metabolically active as white matter. The *top* panel shows two transverse sections of an FDG image obtained on an older instrument, Siemens ECAT 953B, and reconstructed to a final image resolution of approximately 10 mm FWHM (left) and an FDG image from another patient, taken at approximately the same levels, obtained on a more modern instrument, Siemens Biograph 16 PET/CT, and reconstructed to a final image resolution of 5 mm FWHM (right). The *bottom* panels show coronal sections from the same patients using the Siemens ECAT 953B (left) and Siemens Biograph 16 PET/CT (right). The *left* panels show blurring of the activity in grey matter, white matter, and ventricles. The *right* panels show essentially only the grey matter ribbon, whereas the white matter and CSF are at the lower end of the color scale (blue/black). There is still some green at the interface between grey matter and white matter from some residual partial volume effects (Fig. 38.3; *see* complete caption and discussion on p. 712).

COLOR PLATE 13 Avicenna (Fig. 40.3; *see* discussion on p. 732).

Part I
Syndromes—Adult

1
The Mental Status Examination

Hagop S. Akiskal, MD

Abstract The Mental Status Exam 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.

This chapter is derived from the author's teaching experience to medical students, psychiatry residents, and family physicians, and considers both classic 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, white male 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. After 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 woman, 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 a 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 of 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 exclude, 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 exclude somatic contributions is often a 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 schizophrenia 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,

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the mental examination is of particular importance in psychiatry. Accurate description is difficult to obtain without careful and skillful probing during face-to-face interviews. 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 thought 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 that 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 woman). 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. 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 regarding 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—that 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 of 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.

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 after 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 that 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 modem pharmacotherapy and biologic psychiatry, in which syndrome-specific treatments, such as mood stabilizers, selective serotonin reuptake inhibitors (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.

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 the patient or their 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 that 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 as 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, whereas 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 the patient 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 examinations. The differential diagnoses of signs and symptoms discussed throughout this introductory chapter will selectively focus on those concepts that have special diagnostic significance and that seem to be particularly problematic for trainees.

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 of 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, 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-*Diagnostic and Statistical Manual*, 4th edition, text revision (DSM-IV-TR) (2000) (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 seems 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

TABLE 1.1. Mental Status Examination outline.

Areas	Observations
Appearance and behavior	Attire, grooming, appears to be the 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, suicidal/homicidal ideations* 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	

* Changes provided by the editor.

patients, attempting to glean the optimal amount of information necessary for a tentative diagnosis.

5. Areas of the Mental Status

The mental status typically begins with a statement regarding 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 with a careful review of all existing records and proceeds with the areas described below.

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 the same age, educational level, and socioeconomic status. In other instances, the general observation may provide important clues regarding the patient's personality, mood, thought, awareness of social conventions, and ability to function adequately within society.

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.

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 the 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 (1998) 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.

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."

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, whereas, in "flight of ideas," thoughts actually 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 excluded. 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 (1950) coined the term autism to refer to the self-absorption that he thought 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, in which 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 with 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 caused by 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 on 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, sex, 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 in which 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 although 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 himself to be the target of malevolent action; this may be caused by 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.

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, etc. 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 they 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 seem 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 of 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 might 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.

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 regarding 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.

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 a 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") for 5 to 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 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 seems 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 ECT.

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

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 airplane 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 accompanies 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).

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 regarding 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.

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 thought 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).

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, in which 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 very 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, in which there are rapid shifts from elation to irritability to depression; and in acute organic brain disease, in which 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.

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 next consider 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 patients with organic mental disorders 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, seem 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 obsessional patients, 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 of her behavior along those lines.

Delusions can be graded based on 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.

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 Caused by a General Medical Condition

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Abstract The disorders under consideration are the result of identifiable conditions. Historically, an arbitrary distinction has been made between "organic" conditions, associated with a presumably clear pathological basis, and "functional" conditions, or psychiatric disorders that lacked obvious disease processes. Delirium, however, is a disorder of cognitive dysfunction that lacks a well-understood pathophysiology despite unequivocal association with multiple and various medical conditions. More generally, delirium and dementia are frequently complicated by psychopathology (for example, delusions or changes in mood) traditionally associated with so-called functional disorders (schizophrenia and affective disorders, respectively). The organic/functional distinction obscured the propensity of medical conditions (e.g., thyroid dysfunction) to present with psychiatric symptoms that resolved after effective treatment of the nonpsychiatric condition. The nosological conventions of the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision (DSM-IV-TR) (1) allow recognition of syndromes of disseminated cognitive dysfunction, such as delirium and dementia, as well as the psychopathology that is the product of various and multiple medical conditions without obscuring the need to consider these entities in the differential diagnosis of "functional" symptomatology. Regardless of the evolution of diagnostic convention, the illnesses described in this chapter can present to the psychiatrist as a "mental" condition or present to other medical specialists as "medical" conditions.

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

1. Syndromes of Brain Dysfunction Presenting with Global Cognitive Impairment: Delirium

1.1. Definition

Delirium is a disturbance of cognition and consciousness of acute onset (see Table 2.1). The term *delirium is* derived from the Latin *de lira,* meaning "out of the furrow" or off the track. In a classic work (2), Engel and Romano called delirium "a syndrome of cerebral insufficiency." They likened it to syndromes associated with insufficiencies of other organs: renal, cardiac, hepatic, and pulmonary. Lipowski's monograph (3) is comparably titled *Delirium: Acute Brain Failure in Man.* Reduced awareness of the environment is associated with memory impairment, disorientation, language dysfunction, and other types of cognitive impairment. Fragmented patient experiences seem to contribute to perceptual distortions, such as misidentification, illusions, hallucinations, and delusions. Abrupt in onset and usually brief in duration, delirium appears over hours to days and has a fluctuating course. Patient behavior shows wide variability with agitation prominent in some individuals, a quiet listlessness in others, and yet other individuals showing moment to moment variation. Delirium should be distinguished from dementia, a chronic deterioration in cognitive function that is a risk factor for delirium. The terms delirium and dementia are attributable to Celsus (3), a Roman aristocrat writing in the first century A.D., although the Greek Hippocratic case descriptions may also describe both illnesses. It was not until the 20th century that the two disorders were consistently conceptually separated, an inconsistency perhaps resulting from not infrequent co-occurrence of both.

TABLE 2.1. Essential features of delirium.

Decreased awareness of environment (ranging from inattention to obtundation)
Cognitive changes—impaired memory, disorientation, aphasia
Perceptual disturbance—misidentification, misperception, hallucinations
Acute onset of changes in mental function (onset over hours to days)
Fluctuating course

Adapted from DSM-IV-TR (1).

From: S. H. Fatemi and P. J. Clayton (eds.): *The Medical Basis of Psychiatry*

1.2. Etiology and Pathogenesis

Delirium can be evoked by any disease process that directly or indirectly disrupts the integrity of central nervous system (CNS) function. The list of potential etiologies is extensive, if not nearly limitless, although identification of a cause or causes is important to diagnosis and critical to treatment. Sorting out possible causes of delirium is relevant to immediate care because addressing the cause can contribute to the resolution of CNS dysfunction. Furthermore, some causes reflect the efforts of medical personnel to provide treatment (iatrogenic)—for example, multiple and various prescribed medications can cause delirium. Some causes of delirium can be cryptic—the use of illicit drugs, for example—and others, such as those attributable to many toxins, are rare. Finally, delirium has prognostic implications, resulting in longer hospital stays, and greater morbidity and mortality than in patients with the same conditions who do not develop delirium. Unfortunately, the disorder is frequently unrecognized. Applicable diagnostic convention (1) separates conditions responsible for delirium into cases caused by a general medical condition, delirium that occurs as the result of exposure to some substance, multifactorial delirium, and delirium not otherwise specified (see Table 2.2). Considering these broad etiological categories simplifies the process of determining the cause or causes associated with a particular episode of delirium.

Various and multiple medical illnesses result in delirium. The following instances are meant to be illuminative, facilitating the process of determining a diagnosis. Further consideration of illnesses associated with delirium can be initiated by reviewing specific disorders in general medical sources. If specific disorders have a distinctive pathological pathway to delirium, that pathway remains largely unknown. Failure of key organs (e.g., heart, lungs, liver, and kidney) is frequently associated with changes in cognition and perception although, as each organ fails, involvement of other organs is inevitable. Hepatic encephalopathy, reflecting the impact of diverse diseases such as alcohol dependence or hepatitis on the liver, represents a well-described type of delirium with treatment options that can reverse or minimize the impact of liver failure on brain function. Acuity of organ failure may play a role in the appearance of delirium with, for example, patient adaptation to hypoxia from chronic lung disease seemingly more tolerable than decreased oxygen saturation associated with acute pulmonary failure. The compensatory mechanisms that might account for tolerance of chronic changes are unknown. Terminal illness regardless of cause can be associated with delirium. Fluid (e.g., dehydration) and electrolyte (e.g., hyponatremia) disturbances can result in acute CNS dysfunction, with resolution occurring as homeostasis is restored, although restoration of normal cognitive capacity may lag behind correction. Various infections can cause delirium, either directly (septicemia) or indirectly (hypoxia associated with pneumonia). Delirium can reflect intracranial processes even in the absence of focal or lateralizing neurological signs. For example, a seizure can be followed by persistent disorientation and perceptual difficulties. Traumatic brain injury (TBI) is frequently associated with delirium during the acute phase of recovery. Finally, any and all types of medical procedures are associated with an increased risk of delirium. One aspect of recovery from anesthetic agents is a transient interval of impaired cognition; in a small proportion of patients, this transient episode can be relatively prolonged. When associated with agitation, critical care in postprocedure areas can be difficult and recovery delayed. In other instances, delirium will appear hours or days later as the result of procedure complications such as infection or fluid and electrolyte disturbances.

Various substances are associated with delirium (see Table 2.3 for examples). A useful rule is that CNS active drugs or toxins are more likely to be associated with delirium than drugs that act peripherally. Anesthetic agents, as noted above, are thought to be a source of postoperative delirium. More generally, sedative–hypnotic drugs, such as benzodiazepines and related drugs, are associated with delirium as the result of intoxication. Sedative–hypnotic drugs and alcohol are also associated with delirium during withdrawal. Delirium tremens is a classic example of acute brain failure related to alcohol withdrawal that remains a too frequent problem in medical and surgical settings. Furthermore, the multiple pathologies associated with alcohol use (for example, liver failure, seizures, fluid and electrolyte disturbances, and trauma, perhaps requiring surgical intervention) means that

TABLE 2.2. General types of delirium.

Delirium caused by a general medical condition
Substance-induced delirium
Intoxication
Withdrawal
Delirium caused by multiple etiologies
Delirium not otherwise specified

Adapted from DSM-IV-TR (1).

TABLE 2.3. Examples of drugs and other substances associated with delirium.

Alcohol
Analgesics [e.g., non-steroidal anti-inflammatory drugs (NSAIDS)]
Anesthetics (any)
Anticholinergics (e.g., tricyclic antidepressants)
Anticonvulsants (any)
Antihypertensives (e.g., β blockers)
Botanicals (e.g., morning glory)
Corticosteroids
Herbal remedies (e.g., ma huang)
Lithium
Metals and related compounds (e.g., mercury)
Muscle relaxants (e.g., cyclobenzaprine)
Opioids
Organic solvents (e.g., gasoline)
Organophosphate insecticides
Sedative–hypnotic drugs (any)

the patient with delirium thought to be the result of alcohol withdrawal needs a thorough and thoughtful medical evaluation for other causes of delirium. Drugs with anticholinergic properties may also pose an increased risk of delirium relative to other drug classes, such as antibiotics. Many different types of therapeutic agents contain compounds that are anticholinergic. For example, over-the-counter preparations for the treatment of upper respiratory infections such as diphenhydramine can be associated with delirium, perhaps as the result of anticholinergic properties. Relatively specific antihistamines used to treat gastrointestinal (GI) disease (so-called H_2 antagonists) can also be associated with delirium. Herbal preparations, such as those made from jimsonweed or ma huang are associated with delirium (4). Any and all drugs of abuse can be associated with delirium, for most substances, as the result of intoxication. Finally, exposure to various and multiple toxins is associated with delirium. Suspected toxin exposures, either as the result of an accident at home or in the work place or as the result of chronic exposure, accidental or intentional—as the result of work or suspected homicide—benefit from consultation with a toxicologist.

Implicit in the description of causes discussed above is the possibility that a delirious patient will present with multiple examples of illness and/or drug that could be the culprit. At present, a methodology to assign primacy of cause as related to delirium is difficult if not impossible. Presumably, multiple factors converge to precipitate the syndrome. Alternatively, it can be difficult for the clinician to identify and confirm a suspected etiology, relevant to classification of a delirium, as not otherwise specified.

Although the pathogenesis of delirium is unknown, several nonexclusive theories, suggested by observations regarding cause made above, are worth noting. Electroencephalographic (EEG) changes (∼8 cycles per second, slower than observed during normal CNS function) frequently observed during delirium are consistent with cortical dysfunction because the routine EEG primarily measures electrical activity of the cortex. Subcortical structures (reticular formation, thalamus) drive cortical electrical rhythms compatible with the involvement of these structures in delirium. Cortical dysrhythmias suggest that substrate deficiencies, particularly as a consequence of exposure to abnormal concentrations of glucose and oxygen, could be involved. Unfortunately, not all patients with delirium show EEG slowing, and evidence for a missing substrate is lacking in most cases. Fluid and electrolyte disturbances disrupt the ability of nerve cells to initiate/propagate electrical activity ("fire"). Decreased neuronal firing would result in EEG slowing. Perhaps all deliria reflect the relative failure of neuronal firing, although the stereotyped nature of the syndrome suggests that some neuronal systems are more vulnerable than are others. Pathways that involve the neurotransmitters acetylcholine, serotonin, dopamine, and histamine seem particularly vulnerable. Involvement of these somewhat discrete neurotransmitter systems contrasts with work suggesting that the more widespread neurotransmitters γ-amino butyric acid (GABA) and glutamate may be involved in the pathology of delirium. The observation that toxins can cause delirium suggests that a toxin or toxins produced by failing organs remains to be identified. Finally, neurohumoral theories are based on the pervasive impact that substances such as corticosteroids have on CNS function. An adequate pathophysiological theory of delirium would seem to need to weave disparate plausible mechanisms into a final common pathway, a daunting task that remains to be accomplished.

1.3. Epidemiology

The prevalence of delirium is difficult to define, in part, because the disorder is transient. In the general population, the syndrome is likely to be rare because the disorder is usually transient and is associated with serious medical illness requiring institutional management. Much effort has been devoted to estimating the frequency of delirium in hospitalized patients (5), with insufficient attention paid to other institutional settings (e.g., nursing homes) (6). The prevalence of delirium in general medical–surgical inpatient populations at presentation is conservatively estimated at 10 to 15% and slightly higher in the elderly (15–20%). Incident cases during hospitalization are estimated to be roughly similar. Although old age is a risk factor, delirium can occur at any age, with the disorder in children associated with infection and medication (7). Procedures increase the rate of delirium, with invasiveness and extensiveness probably increasing that risk. Intensive Care Unit (ICU) patients frequently experience delirium, with rates as high as 80% reported (8), perhaps reflecting severity and complexity of illness. Sensory impairment, such as that associated with blindness or deafness, preexisting brain dysfunction, polypharmacy, and decreased drug metabolism probably also increase the risk of delirium.

1.4. Pathology

Description of the neuropathological changes associated with delirium is complicated by the duration of the syndrome. Because delirium can result in dementia, the longer the duration from onset to the time of death, the greater the chance that pathological changes are reflective of dementia rather than delirium. In addition, there may be subtle but poorly described differences that reflect the causative agent (9). 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, although, to some extent, this finding reflects cardiovascular effects of these drugs. Microscopic changes may appear strikingly vascular, including hemorrhagic changes (arsenic, lead) and vasculitis (amphetamines). Neuronal loss may be obvious (mercury, lithium), with preferential effects on the pallidum in some

cases (methanol, carbon monoxide) or the cerebellum in other cases (ethanol, phenytoin). Gliosis (lithium, lead) and demyelination (methotrexate) may also be present. Sometimes (calcium oxalate crystals associated with ethylene glycol poisoning), the findings are very specific. The neuropathology literature is limited, perhaps biased toward forensic considerations (homicide, iatrogenic disease), and a more systematic approach to findings observed after the death of delirious patients might be a worthwhile endeavor.

1.5. Clinical Picture

Disturbances of consciousness are central to the clinical presentation of delirium. Difficulty shifting, focusing, and sustaining attention to environmental stimuli are observed in delirious patients. All critical components of attention are altered: alertness, the readiness to respond to stimuli, focus, and selectiveness. These changes have long been described as a "clouding of consciousness." The delirious individual appears to be flooded with incoming stimuli that he or she can no longer structure by selectively attending to some of the input. An extensive examination is likely to be thwarted by a patient who is unable to maintain meaningful engagement with the clinician. The delirious patient seems given to "drifting off" or apparently grasping and responding to only fragments of the dialog. The persistent examiner repeatedly refocuses the patient's attention, a sequence that can be instructive. Interviews with the delirious may be brief. Considerable effort may be expended on eliciting the history from others, such as family, friends, and caregivers. Effort reviewing records to identify putative causes or suggest new diagnostic hypotheses can be critical because the diagnosis directs treatment. Change in arousal and level of vigilance may range from lethargy to agitation. The patient's level of awareness can vary from modest deficits in recognizing details to stupor and, eventually, coma.

Disturbances of cognition are part of delirium. Delirious patients frequently experience *memory impairment.* They manifest difficulties in receiving, retaining, and recalling information, with efforts made to demonstrate these deficits during the evaluation. Techniques include asking the patient to repeat three unrelated words and then recall them several minutes later; serial arithmetic, such as subtraction of numbers; repetition of numbers (think of repeating a phone number); and spelling five-letter words in reverse. Remote memory is often relatively intact (to the examiner's surprise). Patients are subsequently able to recall only bits and pieces of experience while delirious. *Disorientation* to date is also common, disorientation to place is less frequent, and disorientation to self is rare—asking about orientation is an essential part of the clinical examination. *Language impairment* can be prominent but more frequently is a subtle finding. Problems may be noted during the examination, but techniques to elicit language dysfunction include asking patients to name objects or repeat simple phrases. More generally, thought is disorganized and fragmented with defective reasoning. Generally, thought processes are slowed; they may be impoverished as well. The capacity to assess and problem solve is dramatically reduced. Other types of cognitive dysfunction—for example, impaired planning and execution of complex/abstract tasks or executive dysfunction, apraxias or difficulty with complex motor tasks and inability to recognize objects despite intact sensory function or agnosias—can be found on examination but are not necessary or even characteristic aspects of delirium.

Perceptual abnormalities are the most obviously "psychiatric" aspect of delirium. These encompass misinterpretations, illusions, and hallucinations. The patient experience is "oneiroid" or has a dreamlike imagery. Perhaps the decreased consciousness described above results in a struggle to achieve or regain a satisfactory grasp of the situation. 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 misread or 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 of the senses. Hallucinations are false sensory perceptions. Visual hallucinations occur in most deliria (3). Auditory and tactile hallucinations are somewhat less common. Most important, hallucinations are neither diagnostic nor pathognomonic for delirium. In addition, they do not distinguish between delirium and dementia, although these cognitive disorders seem to be more likely to be associated with visual hallucinations than schizophrenia or psychotic affective (mood) disorders, which are probably more likely to be associated with auditory hallucinations. Patients are inclined to believe that the hallucinations are real. Common delusions involve feeling persecuted, seemingly driven by hallucinatory experience sometimes. As a rule, delusions are transient and not very complex in delirium, the opposite of the case frequently observed when examining patients with schizophrenia or psychotic affective disorders. Regardless, psychotic symptoms are troubling to patients and can complicate the delivery of care.

Rapid onset (hours to days) and fluctuating course are important aspects of distinguishing delirium from other psychiatric disorders, particularly dementia. The acuity of delirium is especially helpful in separating delirium from dementia, particularly when the symptom complex is superimposed on a dementia, because dementia is chronic. Fluctuating course is less helpful because patients with delirium and dementia can experience worsening at night ("sundowning"). Fluctuating course is more helpful in separating delirium from schizophrenia and affective disorders because these disorders

tend to be relatively stable, particularly regarding symptoms intrinsic to delirium (consciousness, cognition, and perception). Fluctuating course can trigger recognition of delirium—the practitioner sees a calm, pleasant patient on rounds in the morning and later that day receives notification from caregivers of a crisis because the patient has changed from the examination made earlier in the day, appearing more confused. Reviewing hospital care, by discussion of care with staff and examination of the medical record, is an effective way to detect fluctuating course.

Identification of a cause is critical to diagnosis and treatment. Section 1.2 "Etiology and Pathogenesis" gave various examples. Although the examples are not exhaustive, it is easy to see that removing or decreasing the dose of a diuretic is critical if the patient is dehydrated but may be essential treatment if the delirium reflects cardiac decompensation and fluid overload. Because severity and complexity of illness are likely to increase the risk for delirium, the examining physician seeks to integrate what is known regarding the medical condition or conditions and the treatment of these conditions with the examination, intending to determine which condition or conditions, medication, or substance of abuse seems to be the culprit. This process can reveal the medical wisdom of "addition by subtraction"—reduction of dose or the removal of nonessential medications (subtraction) can elicit a positive clinical response (addition). Sometimes this effort involves the physician primarily responsible for patient care working with the consultant or consultants. Decisions are made regarding primacy of possible causes and then causes are systematically addressed until the patient improves or all possibilities have been excluded. The extraordinarily long list of possibilities suggests the weakness of the latter approach, a comment that generally applies to diagnosis by exclusion. Nevertheless, a systematic approach can lead to detection of unusual circumstances, such as attempted suicide or homicide by poisoning. It may not be possible to assign a cause in approximately 10% of cases of delirium.

Other features of delirium are variably present and considered less specific to the syndrome. Disturbances in the sleep–wake cycle are common. The delirious patient naps or sleeps during daytime hours and is awake "all night long." Insomnia, impaired concentration, vivid dreams, and restlessness are aspects of a prodromal behavioral pattern that may persist beyond the onset of delirium. In general, patients may exhibit increased, decreased, or fluctuating levels of activity during delirium. Some types of delirium, such as delirium tremens, are notable for agitation, but there is not usually an association between the cause and behavioral manifestations. Mood is frequently disturbed. Sometimes there is a connection between mood and activity. Sadness may be accompanied by inactivity and fear associated with hyperactivity. Efforts to associate subtypes of delirium with other clinical aspects of the illness remain inconclusive but promising (10). The International Classification of Diseases, 10th revision (ICD-10) (11) incorporates psychomotor disturbances, emotional disruption, and an altered sleep–wake cycle into the definition of delirium. 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), may be observed or elicited on examination of the delirious patient. Other discrete medical and neurologic signs are comparatively uncommon.

1.6. Clinical Course

Delirium is typically an episodic illness, rather like a short story with a beginning, a middle, and an end, perhaps followed by a denouement. The onset is sudden, fluctuating symptoms are present during the course, and the episode frequently resolves rapidly. Prodromal symptoms are usually appreciated only in retrospect. The severity of symptoms varies, most often being greatest at night, with lucid intervals likely to be observed in the morning. As noted above (section 1.5. Clinical Picture), the unpredictable fluctuations can facilitate detection. Delirium is marked by wide clinical variability, even in the same patient.

Most uncomplicated deliria are short-lived, on the order of a week. Delirium tremens shows this pattern, for example. Recovery is usually complete unless the underlying disorder cannot be redressed. Approximately 10% of patients who suffer delirium during ICU care will meet criteria for the syndrome at hospital discharge. A longer duration, thus, suggests severe and/or complex causative pathology, that the syndrome has shifted to another, more enduring syndrome of brain dysfunction, such as a dementia, or that death is imminent. Delirium seems to increase the risk of institutionalization and death in the months after hospital discharge, although controlling for preexisting illness and severity of concomitant disease is difficult. Furthermore, delirium frequently complicates terminal illness (12), making the final days more difficult for patient and loved ones. Experiencing the psychopathology of delirium may leave the patient puzzled and anxious after recovery. A follow-up visit (the denouement) may alleviate anxiety by describing what is known regarding delirium and relating this information to experience of the patient.

1.7. Laboratory Findings

Specific laboratory studies should be directed by evidence obtained from the history and physical examination for a specific causative drug or physical illness. Because causes can be multiple and the patient examination somewhat unrevealing, systematic consideration should be given to studies such as electrolytes, drug screen, hepatic and renal function studies, oxygen saturation, urinalysis, and an electrocardiogram even if a "cause" can be identified. CNS imaging is usually suggested by focal or lateralizing neurological findings and confirms the location of a lesion or lesions, for example, after a stroke. Absence of a diagnosis after a systematic evaluation (including the tests noted above) may warrant

imaging and examination of the cerebrospinal fluid (CSF), although the yield from these efforts is likely to be low.

Slowing of the EEG, with or without the superimposed fast activity found in hyperactive delirium, is frequently seen in delirium. A diffusely slow tracing can suggest the diagnosis, although slowing can be observed in other circumstances (after a seizure). A normal or fast record does not exclude delirium (13).

1.8. Differential Diagnosis

The differential diagnosis for delirium involves other disorders of cognition, primarily dementia. This distinction should center on the longitudinal course and features of delirium, such as disordered attention and arousal; by contrast, both are associated with memory impairment and perceptual disturbances. As noted above, delirium can be persistent and, thus, have a chronic course similar to dementia. The onset of dementia can be insidious and, thus, hard to define. In circumstances in which the onset of dementia can be defined (after TBI, stroke, or identification or resection of a brain tumor), delirium may precede the chronic deficits associated with dementia. The resolution of fluctuating course and impaired consciousness will mark the onset of dementia, frequently a gradual change that is recognized in retrospect. In some instances, delirium may be superimposed on dementia. The tip-off is an acute worsening of cognition in addition to fluctuating course and changes in alertness. Delirium superimposed on dementia may result in worsening of cognition that does not completely reverse. Finally, dementia can have prominent features consistent with a persistent and long-lasting delirium. This type of course is probably most frequently seen with dementia associated with Lewy bodies. Watchful waiting and a provisional diagnosis are occasionally indicated when diagnosis is uncertain—for example, the patient who presents with features of a delirium but for whom no longitudinal history is available and initial screening fails to identify a cause.

Disorders such as depression, mania, and schizophrenia are usually readily distinguished from delirium. Catatonia, a syndrome of psychomotor symptoms such as immobility, posturing, and mutism (1), can be a complication of these disorders and difficult to separate from delirium. Furthermore, catatonia can be a complication of delirium. As is the case with dementia, patients can have one of these disorders and delirium, the latter perhaps as the result of complications of depression, mania, or schizophrenia, such as dehydration. Suicide attempts can be associated with delirium. In addition, the frequency of alcohol and illicit drug use in this population puts patients at risk for delirium caused by either intoxication or withdrawal. Factitious disorder with psychological symptoms should be included in the differential diagnosis of delirium.

1.9. Treatment

Prevention is the ideal approach. Risk assessment will identify predisposing and precipitating factors; rating scales may facilitate this process (14). Systematic interventions, such as frequent orientation, providing cognitive stimulation, compensating sensory deficits, nonpharmacological management of insomnia, encouraging activity and ambulation, and attention to fluid and electrolyte balance delivered by a special multidisciplinary team yielded modest but definite reductions in rates of delirium and the complications of delirium in a randomized clinical trial (RCT) (15). Another randomized trial involved an overlapping but similar set of clinical interventions initiated by a geriatrician and applied to hospitalized hip fracture patients. This study also showed that the intervention had a positive impact on rates and severity of delirium (16). These interventions are understandable as the consistent application of exemplary medical care and, thus, are very feasible. Difficulty with ascertainment of cases in most clinical settings and resource limitations seem to limit the systematic addition of these experimental approaches to usual hospital care.

Correction of the defects associated with the cause or causes of delirium is essential to treatment. Improvement of delirium is likely to be delayed relative to correction of the problem. Unfortunately, delirium can be a feature of terminal illness and, thus, not correctable. Even for treatable disorders, the patient can be left with deficits (dementia, amnestic disorder). Finally, the search for an etiology is not always a rewarding process.

Attention to the environment can be critical to effective care. Availability of a constant attendant 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. Interventions to prevent delirium, noted above, are also relevant. Restraints are undesirable (17) but can be necessary to prevent the patient from harming self or others and sustaining essential treatment.

Pharmacotherapy is preferable to restraints although medications should be minimized in number and dose, especially when the etiology of the delirium is multifactorial, unclear, or the concurrent illness(es) is severe. Administration of high-potency neuroleptics, such as haloperidol at low doses, can be effective treatment, probably because antipsychotics address perceptual disturbances. Haloperidol is the treatment of choice (18, 19) and can be given by mouth or by intramuscular injection. The drug is also administered intravenously, particularly in ICU settings, although this is not a US 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, and the drug is continued at lower doses until the delirium seems to be resolving, and then tapered to discontinuation. The elderly typically require doses that are more modest (the usual dose is

5–10 mg haloperidol; in the elderly, it is 1–2 mg haloperidol). Haloperidol is associated with dystonic reactions (the involuntary and usually repeated contraction of a muscle or group of muscles), restlessness or akathisia, rigidity like Parkinson's disease, 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 such as dystonia and akathisia when used for other conditions, but the data supporting the use of these compounds in delirium is not as robust as the data is for the use of haloperidol. Haloperidol does not seem to prevent the onset of delirium (20).

Other medications are of uncertain value. A cholinergic theory of delirium, that the syndrome reflects a relative inhibition of central cholinergic neurotransmission, suggests that inhibition of cholinesterase, the enzyme responsible for degrading acetylcholine, could have a positive impact on delirium. Blinded RCTs of the cholinesterase inhibitor, donepezil, a medication that is helpful in dementia of the Alzheimer's type (DAT), showed little benefit in reducing the risk of postoperative delirium for elderly patients undergoing an elective orthopedic procedure (21, 22). Dexmedetomidine, an α_2 adrenergic agonist, has shown some promise as a sedating agent after cardiac surgery compared with alternatives such as the anesthetic, propofol, or benzodiazepines. Further work is necessary to support preliminary observations. Although sedation is undesirable, sometimes use of propofol or benzodiazepines such as lorazepam is necessary because haloperidol and related compounds are not sufficient.

Treatment of sedative–hypnotic drug withdrawal delirium, especially delirium tremens, is best accomplished with benzodiazepines (23). Alcohol withdrawal is one of the most common reasons for delirium in hospital settings and, thus, separating sedative–hypnotic drug withdrawal delirium from other causes of delirium has important treatment implications. The benzodiazepines, lorazepam, diazepam, and chlordiazepoxide, have been used to treat delirium tremens, with lorazepam having the desirable qualities of availability for effective administration by mouth, by intramuscular injection, and intravenous use. Lorazepam does not have active metabolites. Phenobarbital is a barbiturate alternative that is rarely desirable—the long half-life of phenobarbital increases the risk of persistence of side effects common to sedative–hypnotic drugs, such as excessive sleepiness, greater than for the much shorter half-life benzodiazepine, lorazepam. Phenobarbital may have a role in the treatment of delirium appearing in those who are addicted to benzodiazepines or in neonatal abstinence syndrome (24). Finally, haloperidol and other antipsychotics will be used for at least some patients thought to have sedative–hypnotic drug withdrawal delirium because benzodiazepines may not be sufficient, may exacerbate difficulties associated with delirium, such as impaired attention or memory deficits, and because cases may have multifactorial causation rather than simply being the result of alcohol or other sedative–hypnotic drug withdrawal.

2. Dementia

2.1. Definition

Dementia is a syndrome of chronic cognitive deficits. The term dementia is derived from the Latin dement, meaning "to be out of one's mind." Similar to delirium, this syndrome is characterized by global dysfunction, although chronicity is an important distinguishing feature of dementia. Araetaeus, in the second century, associated the global dysfunction characteristic of dementia with aging. Cognitive deficits of dementia cause significant impairment in social functioning—poor relations or disinterest in interactions with others—and occupational functioning. The significant decline from a previous higher level of functioning distinguishes dementia from mental retardation. The DSM-IV-TR criteria for dementia (1) require the development of multiple cognitive deficits as manifested by memory impairment (inability to learn new information and inability to recall previously learned knowledge) and impairment of other domains, such as language (aphasia), movement in the presence of intact motor function (apraxia), inability to identify objects despite intact sensory function (agnosia), or a disturbance in complex cognitive tasks (executive function). This definition may overemphasize the importance of memory deficits because, for example, frontotemporal dementia (FTD) can present with changes in language and executive function. The criteria are descriptive without necessary prognostic implications. Dementia may be transient (chronic drug intoxication, thyroid dysfunction), static (as the result of TBI), or progressive (DAT). Which course applies will reflect the underlying pathology. Nevertheless, dementia is usually irreversible, presumably because of loss of neurons, and frequently has a progressive course.

Given that multiple types of pathology are responsible for the syndrome of dementia, it is reasonable to organize the causes into six groups: 1) DAT, 2) vascular dementia, 3) dementias caused by other general medical conditions, 4) substance-induced persisting dementia, 5) dementia caused by multiple etiologies, and 6) dementia not otherwise specified, following the grouping proposed by DSM-IV-TR (1). At a minimum, this approach organizes information to allow an overview of an increasingly substantial and complex topic. Establishing a diagnosis requires examination of tissue, sometimes obtained by biopsy but more typically at autopsy. Clinicians typically need to make a clinical diagnosis and plan for the future in the absence of pathological confirmation. The groupings recognize the causes of dementia by approximate frequency of occurrence, adding the element of probability to the process of diagnosis initiated by symptomatic observation.

DAT is the most common dementing illness, rather steeply increasing in frequency from rare in middle age until reaching a plateau at more than 10% of the population of people in their 80s. This progressive, fatal neurodegenerative disorder was described by Alois Alzheimer 100 years ago (25). Cerebrovascular disease, associated with frequent morbidity

and mortality, is the cause of vascular dementia. Disorders associated with abnormal movement, such as Parkinson's disease, normal-pressure hydrocephalus (NPH), Huntington's chorea, Creutzfeldt–Jakob disease, and progressive supranuclear palsy (PSP), are examples of types of dementia caused by other general medical conditions. Other conditions, such as TBI, CNS tumor, and CNS infection are causes of dementia at any age. Alcohol is the drug most commonly associated with substance-induced persisting dementia. Finally, DAT and Parkinson's disease are relatively common disorders in the elderly, therefore, it is not surprising that some individuals seem to have a course and pathology that reflect both conditions—a multifactorial dementia.

2.2. Etiology and Pathogenesis

Most dementias reflect the selective loss of neurons. An alternative hypothesis is that disruption of synaptic connections precedes and perhaps accounts for the death of neurons; in either case, the loss of neurons is likely to account for irreversibility. The "reversible" dementias are the exception that demonstrates the importance of neuronal loss. Dementia associated with thyroid dysfunction (either hypothyroidism or hyperthyroidism) presumably represents the chronic impairment of neuronal function without sustained loss of synaptic function, changes in connectivity, or cell death. The essential role of thyroid hormone in cellular function results in diminished neuronal and glial activity that translates into cognitive dysfunction. Dementia from thyroid insufficiency or excess is likely to reflect the greater relative vulnerability of selected populations of CNS cells (those associated with memory, speech) compared with other populations (such as the respiratory center). It seems plausible that failure to address thyroid dysfunction with sufficient rapidity will result in permanent CNS changes. Regardless, the observation is that many patients with "treatable" dementias do not show a return to previous level of cognitive function, reflecting the progression of pathological processes beyond a point of no return, the limited CNS plasticity that comes with aging, the appearance of another common dementing disorder (e.g., DAT), or some combination of these.

Structural changes are frequently obvious on inspection of the brain postmortem (9). Patients with DAT show prominent cortical sulci and narrowing of gyri with relative preservation of the cerebellum. The atrophy associated with DAT usually results in a brain that weighs substantially less than the brain of people without dementia. Gross changes associated with TBI can include obvious atrophy at the point of injury (coup) or on the side opposite of the contact point (contracoup). Vascular disease is thought to cause dementia through the occurrence of multiple cerebral infarcts that may be visible on inspection of the brain. A single stroke can readily be associated with a specific finding characteristic of dementia (e.g., middle cerebral artery thromboembolism is associated with aphasia) but the broad range of findings that constitute dementia are typically the result of multiple vascular events. The loss of blood supply results in neuronal death; current hypotheses regarding the deficits associated with CNS vascular lesions suggest that other factors (glutamate toxicity, calcium imbalance) also contribute to neuronal loss. Although the discrete nature of a stroke suggests that the course of vascular dementia would be punctuated or stepwise, a history of specific events can be difficult to obtain even from collateral sources. At autopsy, the pathology associated with vascular dementia and DAT frequently coexist (26).

Accumulation of toxic proteins is another mechanism that seems likely to account for neuronal dysfunction and death associated with dementia, especially DAT. Cerebral atrophy as the result of neuronal loss is accompanied by microscopic findings (9); other parts of the brain (e.g., cerebellum) appear spared. Several lines of evidence implicate the accumulation of amyloid β (Aβ), microscopically observable as extracellular proteinaceous deposits called plaques, to be the culprit that initiates the pathology of DAT (27, 28). Aβ is a relatively insoluble product of the degradation of the transmembrane amyloid precursor protein (APP). Hereditary or familial Alzheimer's disease, which tends to appear in middle age, is an autosomal dominant form of localized amyloidosis. Patients with hereditary DAT develop 1) plaques in the cerebral cortex with a central amyloid core, 2) neurofibrillary tangles, and 3) cerebral amyloid angiopathy (CAA) involving cortical and leptomeningeal blood vessels. Elderly patients with DAT show the same findings, although careful examination of brain tissue is required to distinguish the findings characteristic of DAT from less prominent changes that occur as the result of normal aging. Mutations in the APP gene result in impaired processing of APP and Aβ accumulation. Down's syndrome (trisomy 21) patients with three APP copies also accumulate Aβ and are likely to develop an early dementia. Aβ is toxic in vitro, and transgenic mice that overexpress APP can mimic the pathology and memory problems associated with DAT. Finally, the apolipoprotein E ε4 genotype is a risk factor for DAT associated with the accumulation of Aβ.

Although accumulation of Aβ could play an essential role in the etiology of DAT, the pathogenesis clearly involves a more complex process (28). For example, neurofibrillary tangles are initially neuronal accumulations of filamentous material, largely hyperphosphorylated tau. As the disease progresses, the neurofibrillary tangles persist in the extracellular space. Distribution of neurofibrillary tangles correlates well with the clinical course of DAT. Initially restricted to a limited subcortical region in the preclinical state, dissemination of neurofibrillary tangles throughout subcortical structures and cortex correlates well with clinical severity. Accumulation of tau in neurofibrillary tangles and as neuropil thread ("tauopathies") has also been associated with other dementing illnesses, such as PSP. Additional ideas about the pathogenesis of DAT focus on vascular changes seen at autopsy, accumulation of aluminum, and viral infection.

Regardless of the etiology, deficits in cholinergic, glutamatergic, serotonergic, and noradrenergic systems are prominent aspects of the pathogenesis of DAT, and strategies augmenting cholinergic and glutamatergic function are important to treatment.

Other types of dementia are also associated with pathological accumulation of proteins (9). Parkinson's disease is a movement disorder associated with the deposition of characteristic neuronal cytoplasmic inclusions, Lewy bodies, and loss of neurons in the substantia nigra. More disseminated distribution of Lewy bodies in additional subcortical CNS structures, such as the nucleus basalis of Meynert and the hypothalamus as well as in cortical areas seems to be a cause of dementia (29). Lewy bodies are partially degraded neuronal cytoskeleton, particularly α-synuclein and ubiquitin. The dementia associated with Lewy bodies can appear as Parkinson's disease progresses or can appear independent of a movement disorder. Similar to vascular dementia, many patients thought to have dementia associated with Lewy bodies also have pathological findings characteristic of DAT.

Prion diseases are the clearest example of dementia as the result of the accumulation of an abnormal variant of a cellular protein (30). A membrane-associated protein of unknown function, the prion protein is widely expressed. The aberrant protein can be infectious, called the scrapie agent, the only known example of a source of infection that lacks nucleic acid. In the affected, posttranslational modification results in a prion protein with a preponderance of β-pleated sheet protein structure that is relatively resistant to degradation. The intracellular and extracellular accumulation of the abnormal prion protein results in several conditions, although the most common is a rapidly progressive dementia. Creutzfeldt described the dementing illness in 1920 and, independently, Jakob described it in 1921; Prusiner was awarded a Nobel prize in 1997 for work demonstrating the infectious nature of the scrapie protein. Gross inspection at autopsy usually reveals relatively disseminated atrophy (9), especially involving the gray matter, although, in some cases, the brain appears normal. Microscopically, the affected regions show relatively evenly distributed intraneuronal vacuoles, leading to another name for the disorder: spongiform encephalopathy. This rare disorder can present with prominent but hard to define symptoms related to depression, anxiety, and psychosis before proceeding, relatively rapidly (over weeks to months), to a typical dementia. The rapidly progressive dementia is frequently associated with CSF elevations of the neuronal protein 14-3-3 and subtle magnetic resonance imaging (MRI) changes; later, the EEG frequently shows biphasic and triphasic sharp wave complexes, appearing every 1 to 2 seconds, superimposed on disorganized background rhythms (31). Most cases are sporadic, thought to be the result of exposure to the abnormal protein; a minority of patients suffer from a familial, autosomal dominant variant that reflects mutations in the prion protein.

Another thread in the etiology and pathogenesis of dementia is the genetic transmission of illness. As noted above, DAT and prion disease can be transmitted as autosomal dominant disorders. Huntington's disease, named after George Huntington, who described the illness in 1872, is an uncommon autosomal dominant disorder that typically presents in mid-life but can present at any time from late adolescence to the early 60s (9, 32). The mutant *huntingtin* gene (33) contains an excess (usually 37 or more copies) of cytosine–adenine–guanine (CAG) trinucleotide repeats ("trinucleotide repeat disorder"). There is a rough inverse correlation between the age of onset, severity, and the number of repeats. Although the protein is widely expressed and of unknown function, the genetic lesion results in the mutant protein containing an excess of glutamine residues ("polyglutamine disorder") and loss of neurons in the caudate nucleus and putamen of the thalamus (9). Huntington's disease and other dementias with prominent subcortical symptoms and pathology are sometimes referred to as subcortical dementias. In addition to characteristic choreiform (reduced movement/rigidity in adolescence) movements, patients present with mood disturbances and cognitive dysfunction, such as impairment in recent and remote memory. The illness involves the frontal lobe and bizarre behavior, perhaps related to psychosis, as well as impaired attention are also part of the symptomatology. Thus, the distinction between subcortical dementias and cortical dementias such as DAT, an illness that involves the hippocampus early in the course, is somewhat arbitrary. Reductions in multiple transmitters, particularly GABA and enkephalin, may account for the complex symptomatology.

FTD is frequently hereditary, usually an autosomal dominant illness, that typically presents earlier than DAT. A symptom complex of prominent executive dysfunction and aphasia associated with affective disruption and behavioral disinhibition yet relative preservation of memory and visuospatial skill in early stages of illness characterizes FTD (34). Pick described cases at the end of the 19th century, noting striking frontal and temporal lobe atrophy. Alzheimer expanded the description of the syndrome by describing microscopic silver-sensitive intraneuronal bodies associated with the disease and, for much of the 20th century, "Pick's disease" was synonymous with FTD. Clinical work at the end of the 20th century suggested that a broader approach was more useful. Death of neurons in the frontal (executive dysfunction, behavioral changes) and temporal (aphasia) lobes results in the characteristic presentation. Mutations in the tau gene seem to explain FTD in some instances (35), although tau is absent from the lesions seen in other cases and additional genes have been implicated in FTD (36).

Environmental sources are also causes of dementia (1, 9). Viral and toxic (e.g., ethanol) etiologies have been implicated in dementia. The pathological processes unleashed by these CNS insults can appear at any time in life, although the elderly may be especially vulnerable. The outcome, neuronal loss and

gliosis, reiterates the importance of cellular processes to the pathology of dementia. Finally, tumors of various types may result in dementia; treatment of the tumor may also contribute to persistent cognitive dysfunction. As with delirium, etiology of dementia often may be multifactorial. Considering the causes of a suspected multifactorial dementia should result in special attention being directed at common pathology, such as that associated with DAT. The multifactorial dementias underscore the fact that disparate pathogenetic mechanisms may each result in the neuronal loss that is likely to be the final common pathway to the clinical syndrome of dementia.

This summary gives a glimpse of the stunning progress, particularly on the descriptive, biochemical, and genetic fronts, made during the last century. Nevertheless, much remains to be learned. Defining the molecular lesions leaves uncertain the path to neuronal death. What also remains puzzling is the delay in onset of these illnesses, given that the genetic lesions are present from inception. Furthermore, several of the disorders are associated with ubiquitous proteins, yet produce relatively specific syndromes. The ability to express the mutant genes in animal models offers the opportunity for advancing the understanding of the pathogenesis of dementia (37). Information garnered to date offers clues for future therapies (38). What is perhaps most frustrating to patients and those who care for them are a host of bizarre behaviors associated with the dementias that are very much the purview of psychiatry and for which current treatment is frequently ineffective.

2.3. Epidemiology

Dementia is associated with aging. This ancient observation is substantiated by community surveys that show the incidence of dementia increasing with age (39–41), although the proportion of the population judged as affected may partly reflect the method of making the diagnosis and the criteria chosen to confirm the syndrome. Some of the elderly have memory complaints and findings that are best described as mild cognitive impairment (MCI). The memory problems reported by these individuals will progress to dementia in a substantial number of cases (42). A small proportion, approximately 4%, of individuals aged 65 years will have symptoms suggestive of dementia, rising to approximately 35% at age 85 years. Considered in a different way, the incidence of dementia doubles for every 5 years of life after the age of 65 years, achieving a plateau at age 85 years. Prevalence rates probably stabilize at approximately age 85 years, strong support for the concept that dementia is an illness associated with aging rather than an inevitable consequence of aging. The majority of affected individuals live in the community, although the most severely compromised are likely to live in institutional settings.

DAT is the most common cause of dementia, accounting for between 50 and 60% of cases of severe dementia. The increase in the prevalence of dementia with aging is largely accounted for by an increase in the prevalence of DAT. In addition to mutations in *APP*, mutations in two genes associated with the metabolism of APP (the presenilins) are linked to early onset DAT; other genes causative of the disorder as it occurs in the elderly may yet be identified. However, only a small proportion of DAT cases will have a clear-cut mode of inheritance. Additional genetic risk factors, noted above, include Down's syndrome and the $\varepsilon 4$ allele of apolipoprotein E. Finally, severe head injury may be an independent risk factor for dementia that suggests shared pathology between DAT and TBI as well as a role for environmental factors in DAT. Protective factors, such as physical and intellectual activity or exposure to nonsteroidal anti-inflammatory drugs (NSAIDs) have been suggested, but evidence for an impact of these and other protective factors is weak, or, in the case of estrogens, discredited because risks outweigh any benefit (43).

Vascular dementia, FTD, and the dementia associated with Lewy bodies account for most of the remaining cases of dementia, with some uncertainty regarding which of these may be the most frequent cause after DAT. Hypertension and hyperlipidemia are common precursors to vascular dementia; smoking and diabetes also increase the risk. Involvement of cardiac and systemic blood vessels is expected, given the systemic antecedents to vascular dementia. FTD and vascular dementia may have a somewhat earlier age of onset than DAT. On autopsy, many cases of these three types of dementia have findings characteristic of DAT. FTD is frequently a genetic disorder.

2.4. Pathology

The gross pathological features of many common types of dementia are described above (Section 2.2 Etiology and Pathogenesis). A chronic subdural hematoma can be a cause of dementia or an incidental finding at autopsy (9). Accumulation of blood in the subdural space, or a subdural hematoma, can be a slowly progressive process associated with cognitive decline occurring over weeks to months in those older than the age of 50 years. Precipitating trauma may be trivial or unidentifiable. Rupture of veins bridging the dura and the brain results in the accumulation of blood. The clot is surrounded by vascular granulation tissue, which forms a pseudomembrane. The lesion may be visualized during life by various imaging procedures or seen at autopsy. Coagulopathies, including therapeutic anticoagulation to reduce the risk of thrombotic complications from disorders such as deep venous thrombosis and atrial fibrillation, increase the risk of subdural hematoma. Finally, the cerebral atrophy characteristic of dementing illnesses such as DAT increases the distance between the dura and the brain and, thus, the risk of subdural hematoma.

Careful consideration of longitudinal course, expecting a more rapid progression if the subdural hematoma is causing or aggravating a dementia; size of the lesion; and associated risk factors (identifiable trauma, coagulation status), are warranted

before subjecting a patient with a chronic dementia to a procedure to treat what may be an incidental finding. For carefully selected patients, evacuation of a subdural hematoma can reverse cognitive function to normal levels or stabilize preexisting impairment.

Many details of the microscopic pathology associated with dementia were summarized in the description of Etiology and Pathogenesis (Sect. 2.2). In addition to plaques, neurofibrillary tangles, and CAA, DAT is associated with granulovacuolar degeneration, Hirano bodies (composed of actin binding proteins) and lipofuscin deposition in neurons (9). CAA is likely to increase the risk of stroke, and the brains of patients with DAT can show macroscopic and microscopic evidence of vascular disease. The microscopic findings associated with DAT and other types of dementia are seen in the brains of otherwise unaffected elderly individuals (44). Microscopic findings tend to be quantitatively more abundant in DAT, and the neuropathologist approaches the diagnosis of DAT in a systematic, quantitative fashion.

Tau has been implicated in the pathology of dementias other than DAT (9). A high density of neurofibrillary tangles and neuropil threads in subcortical regions such as the pallidum, subthalamic nucleus, substantia nigra, or pons may be characteristic of PSP, although the cortex is also involved. Pick's disease, a form of FTD, is associated with the accumulation of argyrophilic (silver loving) spherical inclusions composed of tau and other neurofilaments in the neurons of the frontal and temporal lobes. FTD associated with Parkinsonism is linked to mutations in the tau gene and associated with accumulation of phosphorylated tau in cortical neurons and glial cells. Not all of the inclusion bodies associated with FTD contain tau (36).

Various infections can lead to dementia (9). Human immunodeficiency virus (HIV) infection can cause a dementing illness either as a result of direct infection or because immune suppression predisposes to opportunistic infection by agents such as *Cryptococcus neoformans* and *Cytomegalovirus* or the appearance of a primary CNS lymphoma. Direct HIV infection of the brain may result in microscopic inflammatory changes, such as accumulations of microglia (microglial nodules) and prominent aggregation of lymphocytes around vasculature. These changes are seen in other infectious conditions. More characteristic is a pallor of the white matter or leukoencephalopathy associated with patchy demyelination and white matter gliosis as well as the appearance of multinucleated cells that are positive for the HIV antigens. Unfortunately, correlation between clinical and pathological findings is imprecise. Introduction of effective HIV treatment seems to have had a positive impact, making dementia a less frequent finding (45).

2.5. Clinical Picture

Establishing an *onset* separates dementia from normal aging (1). The process of aging is associated with modest but progressive changes in physical and mental function that occur across the adult life span. Cognitive changes that occur as the result of aging are relatively subtle, almost impossible to define during a clinical examination. Losses of functional capacity associated with aging and frequently accompanying systemic illnesses (e.g., diabetes) are managed by the cognitively intact elderly, indicative of learning new things. Patients with dementia are frequently indifferent to decreased abilities, unaware of the situation or, in some cases, obstructive to compensation for deficits. Although the onset of dementia can be easily defined in some cases (TBI, some instances of vascular dementia), an insidious onset is frequent and perhaps particularly characteristic of DAT. The appearance of multiple types of cognitive deficit after normal development and an interval (usually measured in years) of relatively stable cognitive function distinguishes dementia from mental retardation, important because disorders such as Down's syndrome are associated with both. Delirium should be separable from dementia partly on the basis of the rapid onset of delirium but also because delirium is associated with impaired consciousness. Dementia may be a complication of delirium in addition to increasing the risk of delirium. The recognition of specific types of cognitive deficit is critical to the diagnosis of dementia, and important types of dysfunction will be detailed further (Table 2.4).

Memory impairment is a prominent feature of most types of dementias. Poor memory is a common aspect of the presentation of DAT, characterized by impaired short-term recall as well as difficulty acquiring and retrieving new information. This type of memory impairment is also seen in many cases of MCI (40). Dementia is distinguished from MCI based on the lack of dysfunction seen in patients with MCI; deficits elicited on examination are usually restricted to one area of cognitive performance in patients with MCI. Although MCI is *not* a form of dementia, it can be a prodrome for syndromes such as DAT and vascular dementia—or it can resolve in a small portion of patients. Inquiries can be made regarding acquisition and retention of information regarding recent events, both public (e.g., news stories) and, if such information is available to the examiner, personal details (for example, events of the day before the examination). The examiner may be able to give the patient information regarding current events or the examination (for example, the examiners name or the

TABLE 2.4. Clinical features of dementia.

Memory impairment
Speech difficulties (aphasia)
Problems with movement despite intact motor system (apraxia)
Failure to recognize familiar objects despite intact sensory systems (agnosia)
Problems planning, organizing, sequencing, and abstracting activities (impaired executive function)
Decline from previous level of cognitive function
Significant difficulties with social interactions and occupational skills

Adapted from DSM-TR-IV (1).

room number) and test for the retention of this information. Patient examination to define memory deficits includes asking the patient to remember three unrelated words and expecting retrieval of all three words after a 5-minute delay. Anxiety and poor premorbid memory function will have an adverse impact on performance, therefore, marrying findings on this type of testing with dysfunction elicited during history taking is critical to interpreting examination findings. Progression of illness results in worsening memory impairment, interfering with more remote memories. Tasks such as asking the alert and attentive patient to repeat the presidents of the United States in reverse order, or in the presence of limited education or limited intellect, reverse the names of the months of the year or the days of the week, can be helpful. Alternatively, ability to recall information about relatives degrades over the course of dementia, usually with loss of memory of information about closest relatives last to deteriorate. Knowledge of family matters can be sought during the exam. Absence of such knowledge may be volunteered by or elicited from caregivers.

Problems with *executive function* also occur with most types of dementias, although they are prominent early in FTD. The deficits related to planning, organizing, sequencing, and abstracting information can be elicited during history taking, usually from sources other than the patient. Common tasks that largely reflect executive function include paying the bills, purchasing groceries and other essentials, and maintaining a household. Observations regarding these tasks will frequently need to be sought from relatives or friends because the patient may show little interest in the subject or, because of poor memory, have difficulty recollecting specific details and the course of alteration in function. During the examination, the patient could be asked questions regarding the appropriate actions to take in the event of a fire, heart attack, or a robbery. Alternatively, hypothetical questions could be posed regarding a reasonable response to a broken window, finding a library book, or finding a stamped, addressed envelope.

Aphasia is a prominent early symptom of FTD and can be part of the presentation of vascular dementia; other dementias are more likely to have language impairment appear as the dementia progresses. Aphasia involves the difficulty understanding words (receptive) and/or speaking the correct choice (expressive). Aphasia can be detected during the interview, as the patient has difficulty answering questions (word finding problems). Speech will tend to be repetitive, with heavy reliance on cliches. Paraphasic errors (substitution of one word, sometimes a nonsensical word, for a correct word because of similarity of structure, meaning or phonetic composition) are common. Aphasia may be elicited by asking the patient to read a relatively simple source of information, such as a newspaper headline. *Apraxia*, the inability to perform motor tasks such as buttoning a shirt despite intact motor function, and *agnosia*, the inability to recognize or identify objects such as coins despite intact sensory function, are usually seen as dementia progresses.

Other features of dementia are of less diagnostic importance (DSM-IV-TR criteria) but are frequent and may disrupt caregiving. *Visuospatial deficits* may be seen early in the dementia associated with Lewy bodies (46,47), although most patients with dementia will show indications of *constructional apraxia* as the illness progresses. Drawing the face of a clock, which has prominent visuospatial aspects, has been widely used to test for and estimate the severity of dementia. *Visuospatial deficits* contribute to driving impairment. *Hallucinations*, particularly *visual hallucinations*, are frequently prominent early in the dementia associated with Lewy bodies but are also seen in DAT as the illness progresses. *Delusions*, especially persecutory delusions, can be troublesome because the patient acts on the delusions, sometimes putting the patient and/or others at risk of harm. Changes in personality with prominent *apathy* and *irritability* may be a troublesome part of the presentation and course of DAT. Dementia can present with depression, or symptoms of depression can appear during the course of dementia. *Mood lability*, engaged and pleasant one moment followed by sadness and tears or anxiety and inexplicable rage the next, is more common than mood disorders, but can be bothersome to those close to the patient. Findings associated with trauma, including peripheral neurological deficits, are frequently seen after TBI, but, for many other dementias, the initial neurological examination can be unremarkable. So-called "*primitive reflexes*" (for example, suck and snout), named in this fashion because they are present at birth but are usually lost with CNS maturation, may appear as the dementia progresses (frontal lobe release signs). *Disturbances of posture*, *gait*, *and muscle tone* are common as dementia evolves; these findings will precede the development of dementia in patients with Parkinson's disease. *Seizures* can be a consequence of TBI and are not infrequent in DAT and vascular dementia. Purposeless *agitation* can complicate the course of dementia, agitation that may not respond readily to redirection or that results in *aggression*. Disturbances in the *sleep–wake cycle* complicate management because patients are awake much of the night and doze during the day, exhausting caregivers. Finally, a host of peculiar behaviors can bedevil the care of patients with dementia. These include but are not limited to persistent and repetitive screaming, whistling, grunting, unexpected profanity, obscenity, and masturbation. Although unusual, these problems can lead to institutionalization because of persistence and intolerability.

2.6. Clinical Course

The initial presenting features and the ensuing course of a dementia are, to some extent, functions of the specific disorder, although the end stage of the progressive disorders is very similar. DAT tends to have an insidious onset and prominent memory problems at presentation. It is not unusual for the history to reveal that symptoms have been present

for 1 to 2 years before seeking medical attention. After diagnosis, DAT will progress to death over an interval of years. Although the range of duration is wide, most patients will be dead within 5 to 10 years after diagnosis. Earlier onset is associated with more severe illness at presentation and more rapid deterioration. The initial phase of DAT is dominated by memory problems and indifference. At the time of diagnosis or shortly thereafter, the progression of the illness and loss of function needs to be discussed with the patient and significant others. This somewhat unpleasant process will encourage sensible planning and at least some anticipation of patient wishes before the illness robs the patient of the ability to participate effectively in discussions regarding care. Caregivers can usually assist the patient in the early stages of the illness with compensatory efforts (lists and other cues to enhance memory, simplification of the environment) (48, 49); and management at home is almost always feasible (50). The midstage of DAT is characterized by the obvious appearance and prominence of the other diagnostic features of dementia. The patient needs assistance with evermore activities of daily living (ADLs). At least half of the patients in the midstage of illness will experience delusions and hallucinations, the latter typically visual, and both frequently transitory. Worsening at night ("sundowning") can also be troublesome. The end stages of the illness are associated with an inability to care for self, inability to recognize others (including spouse and children), and inability to process information from the environment. Bowel and bladder control will be lost. Some patients will have a guardian or other legal representative manage their affairs, usually because finances need management or because family members disagree about care approaches, and sometimes both, but most patients will be assisted based on patterns established earlier in the course of illness. Most patients will be institutionalized in the late stages of illness 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. The appearance of disruptive behavior at any stage complicates management and hastens patient institutionalization and demise. Although the course described here reflects DAT, the end stage of all progressive dementias appears very similar. DAT patients have an earlier death than individuals without dementia, frequently from infectious illnesses such as pneumonia ("the old man's friend").

Many other types of dementia appear earlier in life than DAT. Focal neurologic abnormalities at presentation may be characteristic of vascular dementia, and this dementia may have a more "step-wise" progression than DAT. The behavioral disturbances associated with FTD may result in earlier institutionalization than is seen with DAT. The dementia associated with prion disease shows a particularly rapid course (death in months). By contrast, dementia as the result of TBI can be stable for years, although at least some patients subsequently develop a progressive decline with a course and pathological features rather like DAT.

2.7. Laboratory Findings

A very small proportion of patients with dementia will have conditions that are potentially treatable, resulting in reversal to normal or stabilization of cognitive function. Some of these conditions are confirmed or detected by laboratory tests. Laboratory screening for thyroid disease and B12 deficiency are warranted (51, 52). Serology for syphilis may be warranted, although neurosyphilis is very rare and some common conditions (for example, chronic liver disease) predispose to false positive results. Elevations of CSF 14-3-3, MRI scan findings, and EEG changes seen during the course of the dementia associated with the aberrant prion protein assist with the separation of Creutzfeldt–Jakob and related dementias from other dementing illnesses (31). A variety of other laboratory tests—complete blood count (CBC), and blood glucose, blood urea nitrogen/creatinine, and serum electrolyte levels, for example—can be performed. To the extent that these tests are useful, they are most likely to detect an unsuspected but probably manageable concomitant condition or conditions. The history and physical examination will frequently have suggested the potential for problems associated with laboratory measures beyond B12 deficiency and thyroid dysfunction. The course after correction of laboratory result abnormalities to physiological normality will indicate the impact that any laboratory result abnormality had on cognitive dysfunction.

Structural lesions of the brain can present with dementia—chronic subdural hematoma may be detected by various imaging techniques and brain tumors can rarely present with cognitive impairment consistent with dementia. A noncontrast computed tomography (CT) or MRI scan is advised (52), although yield is low. Another illness that can be detected by CNS imaging is NPH. NPH presents clinically as a triad of cognitive disturbance, difficulties walking ("sticky" gait), and urinary incontinence; sometimes the patients comes to attention because of apathy and depression. The name is somewhat of a misnomer—although CNS pressure is typically unremarkable at the time of a lumbar puncture, longitudinal consideration of pressure indicates intermittent increases. Most cases are idiopathic, although sometimes NPH is associated with a history of subarachnoid bleeding. CNS imaging reveals enlarged ventricles, with particular prominence of the frontal and temporal horns. Cisternography shows accumulation of isotope in the ventricles with failure to redistribute over the subsequent 2 to 3 days. Unfortunately, the results of CNS shunting to maintain stable pressure have not been impressive, perhaps because the adverse effects on cognition are not as readily reversible as the adverse effects of NPH on gait and bladder function (53). Complications of shunting include infection and subdural hematoma, and patients should be carefully selected for shunting.

Overall, the course of dementia will determine the worth of CNS imaging, with more rapid progression of symptoms (over weeks to months) suggesting the importance of radiological evaluation. Unexpected neurological findings should

also prompt consideration of imaging. Similar comments apply to routine examination of the CSF. The role of laboratory tests in the diagnosis of dementia will hopefully change—structural and functional imaging, CSF findings, and genotyping offer tantalizing possibilities of improving the diagnosis of dementia yet have not been shown to have sufficient sensitivity and specificity for routine use.

2.8. Differential Diagnosis

The most important disorder to be distinguished from dementia is depression. Perhaps 5% of patients referred for a suspected diagnosis of dementia will have depression. Separating dementia from depression can be difficult. Patients with depression tend to complain about memory problems more bitterly and frequently than patients with dementia, who tend to be apathetic or deny memory problems despite objective data to the contrary. Mood disturbance is more pervasive and sustained in depression whereas patients with dementia are subject to mood lability. Profound sadness and anergia associated with depression can leave the patient unable to perform ADLs, thus, appearing like the executive dysfunction associated with dementia. There may be a preceding history of mood disorder, providing a clue to a diagnosis of depression; a family history of depression can also be used in this fashion. Mimicry of dementia by an affective disturbance usually begins more discretely and progresses more rapidly than dementia. Depression can be associated with variable but overall poor performance during the examination, usually because of inadequate effort. The term *pseudodementia* has been used to describe cognitive dysfunction appearing in depressed patients (especially the elderly). Dementia and depression are common illnesses in the elderly and chance overlap will be common. Some dementias (FTD, Huntington's dementia, and the dementia associated with prion diseases are examples) are notable for presenting with affective symptoms. A small proportion of patients with DAT may present with depression, but the symptoms evolve into DAT. Regardless of the role of depression in the presentation of dementia, affective illness can complicate the course of dementia. The observations made by significant others and caregivers during the course of illness coupled with repeated examinations are critical to decisions regarding diagnosing and treating depression in patients with dementia.

Remaining psychiatric diagnoses relevant to the differential diagnosis of dementia include delirium, schizophrenia, and amnestic disorder. In general, these illnesses are associated with an apparent loss of intellectual abilities. Distinguishing dementia from delirium and the potential for reciprocal relationships between these disorders has been reviewed above (section 1.8. Differential Diagnosis). Emil Kraepelin first called schizophrenia by the term *dementia praecox*. Work that is more recent suggests that approximately 25% of patients with schizophrenia will have troublesome cognitive deficits, independent of psychotic symptoms that are more characteristic, and reflecting memory and executive dysfunction. Although schizophrenia usually has an onset between the late teens and late 30s, a small proportion of patients will have an onset at other times during the lifespan, with a modest excess in late life. Some cases of late-onset schizophrenia will progress to a clear dementia. Finally, as patients with schizophrenia live longer, dementia may appear because the risk of dementia rises as a population ages.

Amnestic disorder is impairment of memory only (Please see Chapter 3). Although there are multiple plausible causes, alcohol is the most important cause via thiamine deficiency and the induction of a delirium (Wernicke's encephalopathy) followed by persistent amnesia (Korsakoff's psychosis). The restriction of cognitive impairment to memory deficits distinguishes amnestic disorder from dementia associated with alcohol. Alcoholic dementia tends to have an earlier onset than DAT (54).

Making a diagnosis of dementia should be followed by consideration of a specific type of dementia, a clinical diagnosis that is intended to reflect pathology and predict prognosis. This task is especially difficult because the prevalence of DAT means that atypical presentations of DAT will be almost as common as many other types of dementia. The earlier age of onset of other types of dementia is an important clue to separating each type from DAT (54). Family history suggestive of a specific type and mode of inheritance can also be important. Many of the other relative distinguishing characteristics of specific types of dementia have been delineated in the information presented above and will not be repeated. Separating types of dementia will be particularly difficult for the generalist because the rarer types of dementia will not be seen over the course of a career. Finally, dementia can have multiple etiologies, usually DAT and another type, because of the high prevalence of DAT. The implications for treatment of specific types of dementia make this difficult task important.

2.9. Treatment

Explanation of the diagnosis, prognosis, and discussion of planning for the future lead to behavioral interventions. As is often the case with chronic and progressive disorders, the essential information may need to be repeated; sometimes other resources (55) are critical. Memory support (lists, cues) can be helpful to the patient (48,49). Engagement in mentally stimulating activities (hobbies, reading, discussion of current affairs—whatever has interested the patient in the past) may sustain cognitive function. Caregiver support has been shown to enhance the quality of life and perhaps have an effect on progression (50). The home environment can be simplified and modified (e.g., redesign of bathroom to include features such as bath rails) to minimize adverse impact on cognition and reduce risk of complications such as falls. Respite interventions (adult day care, vacations away from the patient) that allow caregivers time away from the patient with dementia can be critical to sustaining the patient in the home environment.

Finally, early explanation of the possibility of bizarre, even life-threatening, behaviors provides the bewildered caregivers information needed to apply consistent, persistent redirection and invoke appropriate emergent assistance if and when such interventions are necessary (50).

Delaying the progression of dementia is the promise of current pharmacological interventions for dementia. The cholinergic deficits associated with DAT suggested a role for cholinesterase inhibitors. Current medications (donepezil, galantamine, rivastigmine, tacrine) enhance function and delay progression for a portion of patients with mild to moderate dementia in RCTs, although response is rarely more than modest and no clear benefit may be demonstrated (43,56). These drugs may have a modest impact on the behavioral disturbances associated with DAT. These drugs may delay the characteristic decline but certainly do not reverse it in a clinically meaningful way. Although generally well tolerated, side effects such as GI problems lead to discontinuation of the drugs by some. Donepezil has the advantage of once a day dosing. Rivastigmine and galantamine have effects on cholinergic systems beyond those noted for donepezil and are equally effective. Tacrine is available but is not considered in current treatment guidelines (43, 56), probably because the drug is frequently (∼25% of treated patients) associated with liver dysfunction; this drug should be avoided. One cholinesterase inhibitor can probably be substituted for another, with some benefit in the event of intolerable side effects from the initial choice, but data suggesting that substitution for lack of benefit will result in improvement is not very compelling. Other types of dementia, such as the dementia associated with Lewy bodies, vascular dementia, and TBI, may also benefit from cholinesterase inhibitor treatment. Cholinesterase inhibitors seem unlikely to alter the conversion of MCI to DAT (57).

Inhibition of glutamatergic receptor function can also delay progression of DAT. Memantine causes a use-dependent blockade of a class of glutamate receptors, the *N*-methyl-D-aspartate (NMDA) receptor. This antagonism has a positive effect on the illness by disrupting glutamate excitotoxicity or by enhancing hippocampal function. Some patients with moderate-to-late DAT show modest benefit from this medication in RCTs (43, 56). Memantine may be beneficial for vascular dementia. Side effects, largely headache and GI, are associated with intolerability for some patients. Some patients benefit from an additive interaction between cholinesterase inhibitors and memantine, although overlapping side effects can limit use of the combination. Perhaps the most difficult decisions regarding the use of currently available medications for the treatment of dementia is defining the benefit to the patient and, if no benefit can be defined, deciding if and when it is appropriate to stop the drug. Involvement of caregivers is likely to be critical to this decision.

Other agents are of interest but of uncertain benefit at best (43). Small doses of levodopa may be helpful for the dementia associated with Lewy bodies. Vitamin E, touted as an antioxidant, may have an effect on the progression of dementia, although large doses may be required and large doses (greater than or equal to 400 U/day) seem to be associated with increased all-cause mortality. No treatment has been shown to have preventive effects. NSAIDs and statins are of uncertain benefit at best and should not be routinely prescribed to prevent dementia or for the treatment of dementia. Advice regarding the treatment of Huntington's disease is not well supported by evidence (58). Novel approaches are focused on preventing or attacking plaque and tangle formation, plausible leads to treatment of DAT, and, in the case of tangles, perhaps other types of dementia because of the involvement of tau in dementias such as various types of FTD.

Disruptive behaviors are part of the course of many dementias, but can be difficult to treat. The first step is caregiver education, as noted above. Redirection, reassurance, and, if the behavior does not put the patient or others at risk, ignoring the behavior are appropriate options even if the problem is bizarre or socially inappropriate. Rapid onset of new behaviors, such as uncharacteristic agitation and aggression can indicate another condition, perhaps delirium or intolerable pain associated with an unsuspected medical condition, such as a fracture that occurred as the result of an unwitnessed fall. The obvious approach is correctly identifying the new condition and applying appropriate treatment. Unfortunately, the limited ability of the demented patient to provide information can make determining the precise cause of worsening of chronic problems or onset of new disruptive behavior difficult. Life-threatening situations will require transient, emergent intervention with sedating drugs (antipsychotics, such as haloperidol, and/or sedative–hypnotic drugs, such as lorazepam) and/or use of restraints. These interventions may be necessary to provide essential or life-saving care, even if a cause is identifiable and correctable. Restraints are especially undesirable. After the crisis has passed, medications used to manage the situation should be discontinued as rapidly as feasible. Persistent disruptive behavior is optimally managed with drugs used in the treatment of dementia, although the impact of these drugs is uncertain at best (43). Persistent psychotic symptoms may require treatment with antipsychotics (59), although these medications were not superior to placebo in a well-powered RCT involving community-dwelling patients with dementia (60). The risk posed by psychotic symptoms will be a key element in the decision to use antipsychotics, because the drugs tend to have adverse effects on movement, increasing the risk of falls, and seem to be associated with a modest increase in the risk of adverse vascular events. Antipsychotics, except for the difficult-to-use drug clozapine (associated with special risks and monitoring procedures), are contraindicated for patients with dementia associated with Lewy bodies and in the presence of Parkinson's disease. Antidepressants such as trazodone and citalopram are also used to treat disruptive behaviors associated with dementia, although benefits are uncertain at best. Selective serotonin reuptake inhibitors

(SSRIs) may play a role in the treatment of FTD. Treating depression that is part of the presentation or develops over the course of dementia is probably useful regardless of the type of dementia. Chronic treatment with benzodiazepines and related compounds is undesirable for demented patients in the absence of all except the clearest of indications because these drugs have an adverse effect on memory and increase the risk of falls. Ramelteon, a melatonin agonist, may be useful in the treatment of insomnia that is part of dementia, and buspirone may be helpful for anxiety. Institutionalization is unfortunately one consequence of unmanageable behavior, probably occurring earlier than for patients without such behaviors. Disruptive behavior degrades the quality of life for patients with dementia and those who love them—better solutions are needed for this complex set of problems.

3. Mental Disorders Caused by a General Medical Condition

The conceptual theme that underlies this chapter is that various and multiple medical conditions can cause psychiatric syndromes, disorders that are seen by psychiatrists or are referred to psychiatrists for consideration of diagnosis and treatment. The information presented regarding delirium and dementia emphasized the connection with medical conditions. This link persists beyond delirium and dementia. Standard nosology (1) recognizes the possible contribution of various medical illnesses to a variety of additional adult psychiatric syndromes (see Table 2.5).

3.1. Definitions and General Observations

The creation of mental disorders caused by a general medical condition was one aspect of the operationalization of psychiatric diagnosis associated with DSM-III (61). Perhaps the conceptual seeds were sown in the criteria for psychiatric diagnosis proposed in 1972. The so-called Feighner criteria (62) included secondary depression, depression that could arise in the context of a life-threatening or incapacitating medical illness. DSM-III elaborated an association between medical disorders and mental illness into four disorders, defined as organic hallucinosis, organic delusional syndrome, organic affective syndrome, and organic personality syndrome. These "organic" syndromes were judged to be etiologically related to a specific organic factor but free of clouding of consciousness and significant intellectual impairment. The concept of mental disorders versus medical conditions was so robust that the diagnostic range was expanded in DSM-IIIR (63) and again in DSM-IV-TR (1). In addition, DSM-IV-TR eliminated the "organic" designation.

TABLE 2.5. Mental disorders caused by a general medical condition.

Psychotic disorder caused by a general medical condition
Mood disorder caused by a general medical condition
Anxiety disorder caused by a general medical condition
Sexual dysfunction caused by a general medical condition
Sleep disorder caused by a general medical condition
Catatonic disorder caused by a general medical condition
Personality change caused by a general medical condition

Excluding syndromes with predominant cognitive dysfunction, such as delirium, dementia, and amnestic disorder. Adapted from DSM-IV-TR (1).

The use of mental disorder caused by a general medical condition requires several judgments on the part of the diagnostician. The criteria recognize the need to identify a specific medical condition based on the history, physical, and/or laboratory tests. Consideration of a myriad number of possibilities is plausible but, rather, as was the case with delirium and dementia, some conditions have associations with mental disorders that are relatively well supported by the literature and, thus, will receive the most attention. Next, the clinician has to have confidence that the psychiatric symptoms can be linked to a known or to-be-determined medical problem. Concurrent longitudinal course is helpful, but mood and psychotic symptoms can be attributable to disorders such as systemic lupus erythematosus (SLE), even when the mood and psychotic symptoms are present months before other manifestations of the illness. Alternatively, psychosis has long been known to be a late complication of epilepsy (64), perhaps reflecting the long-term impact of difficult to control seizures. Associations may be bidirectional: the risk of developing depression seems to be increased in patients who suffer from preexisting migraine headache, and preexisting depression seems to increase the risk of developing migraine. More generally, previous episodes of mental illness and perhaps family history should suggest caution regarding associating a particular medical condition, no matter how plausible the attribution otherwise seems, with current psychiatric symptoms. In the presence of a well-defined preexisting mental illness, the medical illness associated with a mental disorder is perhaps more worthy of consideration as exacerbating the preexisting mental illness.

Depression and anxiety are relatively common problems, so that an association between a medical condition and either depression or anxiety should rise to rates that exceed the population base rate (in the case of depression, for example, significantly more frequent than an approximately 10% lifetime prevalence). Experimentally, comparison of the rate of systematically determined depression or anxiety observed in a population afflicted with a particular medical condition with rates of depression or anxiety in a "healthy" population supports a connection between the medical condition and depression or anxiety. Unfortunately, this methodology will be difficult to apply to relatively rare psychiatric conditions, such as catatonia, on the one hand, or to relatively rare medical conditions, such as paraneoplastic syndromes, on the other hand. The presence of almost any medical condition seems to increase the risk for depression and anxiety.

The face-valid explanation is that medical illnesses remind us of our mortality, a depressing and anxiety-provoking circumstance. Alternatively, or perhaps in addition, adjustment to and compensation for most illnesses may result in systemic changes (for example, changes in the hypothalamic–pituitary–adrenal [HPA] axis) that are associated with depression and anxiety. Depression shares symptoms with many medical conditions, most notably, fatigue. In some cases, the mental disorder and the medical condition can be hypothesized to share pathology. Depression and coronary artery disease may be associated in a reciprocal fashion because they are hypothesized to share a role for catecholamines in the pathogenesis in each, for example. The reciprocal relationship between migraine and depression may involve serotonin. Examples given above and in the sections that follow are robust associations that merit diagnostic and treatment consideration. Nevertheless, making a diagnosis of a mental condition associated with a medical condition entails the judgment that the presenting symptoms are not caused by an analogous psychiatric condition (e.g., the diagnosis should be major depression rather than depression caused by a medical condition).

Other features of mental disorders associated with medical conditions contribute to diagnostic attribution. For example, as already noted in the Sect. 2 on dementia, onset of schizophrenia is relatively rare in the middle-aged and elderly population. Appearance of psychosis after approximately age 40 years should prompt a more thoughtful examination for neurological findings and consideration of screening laboratories, such as imaging studies. Similar concepts apply to the onset of panic disorder, although, here the range of possibilities is broader. In both instances, substance use (heavy use of alcohol or unsuspected use of stimulants) should be a prominent aspect of the differential diagnosis. Subthreshold syndromes—several symptoms of depression or an unusually long duration to worsening of panic symptoms, for example—may also be a clue to association between a medical condition and a mental disorder. The diagnostic criteria for each of the mental conditions caused by general medical disorder save one (sexual dysfunction) specifically exclude the appearance of the symptom during the course of a delirium. Finally, the symptoms associated with each of the mental conditions should cause definable distress or impairment in social, occupational, or other important areas of functioning, presumably independent of the medical condition. This standard seems especially relevant to sleep and sexual disorders, because occasional dysfunction is probably common and treatment interventions may pose more risk than is worth any benefit.

3.2. Psychotic Disorder Caused by a General Medical Condition

Hallucinations and delusions are the psychotic symptoms that dominate the clinical picture with the diagnostician expected to select the "predominant" type of symptom if both are present (1). The parallel psychiatric disorders are presumably schizophrenia and related syndromes. The vast majority of cases of schizophrenia have an onset between the ages of 15 and 40 years; prominent psychosis outside of this age range is a prompt to consider a general medical condition. Within the typical age range for onset of schizophrenia, perhaps 5% of new cases will be caused by a general medical condition. At any age, prominent nonauditory hallucinations suggest the possibility of a general medical condition. Separation from delirium is especially important, given the frequent prominence of perceptual disturbances during episodes of delirium—acuity of onset, disturbance of consciousness, and fluctuating course are useful markers of delirium. Medical illnesses associated with psychosis include SLE, endocrine conditions such as an excess or deficiency in thyroid hormone (hyperthyroidism and hypothyroidism, respectively), CNS tumors, migraine, and various metabolic conditions (32, 64). Partial complex seizures (temporal lobe epilepsy) seem to be preferentially associated with olfactory hallucinations and perhaps religious delusions. Multiple and various medications, illicit substances, and toxins have been associated with psychosis. Matching exposure to or, in the case of some abused substances (e.g., alcohol), withdrawal from the agent, are clues to a role for the substance in psychosis. In some cases, separating the role of the medical condition from the role of a medication used to treat that condition can be difficult. Antipsychotics presumably contribute to amelioration of symptoms, particularly if treatment of the medical condition is not sufficient or delay in response to the medical intervention puts the patient or others at risk.

3.3. Mood Disorder Caused by a General Medical Condition

The parallel affective syndromes include depression, mania, and a mixture of both—these descriptors apply to subtypes of mood disorders caused by a general medical condition (1). In addition, the depressive syndromes associated with medical conditions are separated into patients with a general medical condition and with symptoms meeting criteria for a major depressive episode or individuals with prominent sadness despite not meeting criteria for depression, presumably like dysthymia. Onset of mania in late life (after the age of 50 years) is frequently associated with various medical conditions (65), although, in the elderly, information regarding past psychiatric illness may be difficult to obtain or uncertain. Longitudinal course is relevant because previous episodes of mood disorder suggest that the association between a general medical condition and a mood disorder is more likely contributory or complicating but less likely to be etiologically related. Thyroid disorders, both hypothyroidism and hyperthyroidism, are notable for causing mood symptoms and complicating affective illness (1, 32). Pancreatic cancer can present with depression. Multiple sclerosis, CNS tumors, and stroke have also been associated with mood disorders.

Cushing's syndrome, the result of an excess of corticosteroid, is very frequently, although not invariably, associated with depression. The prominent association between excess corticosteroid and mood disorders supports a role for the HPA axis in depression that occurs independent of a general medical condition. Substances such as alcohol, illicit drugs, and toxins have been associated with mood disorders. Beyond correction of the medical condition associated with a mood disorder, antidepressants may be useful treatment of depressive symptoms. Treatment of mania and mixed states caused by a medical condition with bipolar disorder pharmacotherapy (for example, lithium) may be more problematic because of the narrow therapeutic index of these agents. Antipsychotics, especially newer agents (so-called atypical or second-generation drugs), are helpful in the treatment of bipolar disorder and perhaps in the treatment of mania and mixed states caused by a general medical condition.

3.4. Anxiety Disorder Caused by a General Medical Condition

Anxiety disorders caused by a general medical condition are specified as being predominantly associated with panic attacks, generalized anxiety, and obsessive–compulsive symptoms (1). These subtypes reflect prominent types of anxiety disorders. In general, anxiety disorders tend to have an onset in the age range of late teens to early 30s and are usually more common in women than men. Cardiovascular disorders and respiratory conditions are common illnesses associated with anxiety caused by a medical condition. Rarer conditions, such as pheochromocytoma (32) and porphyria, have also been associated with anxiety conditions. Finally, CNS conditions such as neoplasms are associated with anxiety disorders. Acute onset of anxiety should prompt consideration of delirium. Depression can have anxiety as a prominent symptom, is a frequent complication of many medical disorders, and is also an important alternative diagnosis as an independent illness. Medications such as sympathomimetics and anticholinergics, alcohol (especially during withdrawal), and illicit drugs such as cocaine (during intoxication), as well as toxins have also been associated with anxiety disorders and are, thus, part of the differential diagnosis. In addition to treatment by resolution of the medical condition, some antidepressant types, such as SSRIs and tricyclic antidepressants, as well as benzodiazepines, are effective treatment of anxiety disorders and presumably have a place in the treatment of anxiety disorders caused by a general medical condition.

3.5. Sexual Dysfunction Caused by a General Medical Condition

Sexual dysfunction is further specified by sex and, for erectile dysfunction and dyspareunia, restricted to men and women, respectively. Disruption of neural signals (peripheral neuropathy) and blood flow (vascular disease) to the genitals are prominent causes of sexual dysfunction. Pelvic (infection, neoplasms) and genital (atrophic vaginitis, Peyronie's disease) disorders are obvious sources of sexual dysfunction caused by a general medical condition. Sexual disorders can be the result of surgical interventions (episiotomy, prostatectomy). Anxiety regarding sexual function can be the cause of sexual dysfunction and frequently complicates sexual dysfunction caused by a general medical condition. This reciprocal relationship makes estimating the relative proportions of sexual dysfunction caused by medical conditions, caused by a substance and solely reflecting a psychiatric disorder difficult. Laboratory tests such as determining the presence of nocturnal penile tumescence during the assessment of erectile dysfunction and colposcopy/cystoscopy for dyspareunia can play a critical role in diagnosis and treatment, although a history and physical examination are essential and frequently sufficient. Depression and alcohol use are associated with sexual dysfunction. Cyclic guanosine monophosphate-specific phosphodiesterase type 5 (PDE 5) inhibitors (sildenafil, vardenafil, tadalafil) have revolutionized the treatment of erectile dysfunction (66). Hormone replacement therapy is sometimes indicated as treatment, based in part on supporting laboratory tests and in part on patient participation in comparing typically modest benefit with known risks (e.g., cardiovascular disease).

3.6. Sleep Disorder Caused by a General Medical Condition

The major types of sleep disorders include insomnia, reflecting difficulty falling asleep, sustaining sleep, and/or awakening without a refreshed feeling; hypersomnia or excessive sleepiness; and parasomnias, disturbed behavior that occurs in the context of sleep or the transitions from wakefulness to sleep and/or from sleep to wakefulness (1). In addition, there is a mixed type—for example, patients with Klein–Levin syndrome, a rare periodic disorder of unknown etiology associated with hypersomnia, hyperphagia, and hypersexuality, can have excessive sleepiness and nighttime eating or a parasomnia and, thus, a mixed type of sleep disorder caused by a general medical condition (67). Respiratory conditions (chronic obstructive pulmonary disease [COPD], asthma) and cardiovascular disorders are frequently associated with insomnia. In addition, various and sometimes common musculoskeletal conditions, such as rheumatoid arthritis, are associated with insomnia, probably reflecting chronic pain. Viral encephalitides can be associated with hypersomnias. Cerebrovascular disease involving the upper brainstem can be associated with sleep disturbances. Prader–Willi is a rare genetic disorder (chromosomal abnormalities of 15q11-15q13) especially involving the hypothalamus, with childhood onset of symptoms that include hypersomnia, hyperphagia, impaired intellect, and obesity (68). Obesity and aging play a more general role in sleep disturbances, both associated with poor quality sleep. In addition to primary sleep disorders,

depression is a common syndrome associated with disturbed sleep and, thus, an important aspect of the differential diagnosis. Mania, delirium, and dementia also are associated with sleep disturbances. Prescribed drugs (stimulants), over-the-counter medications (antihistamines such as diphenhydramine) and commonly used substances, both legal (alcohol, caffeine) and illegal (sympathomimetics such as cocaine), are associated with sleep disturbances and, thus, should be considered as part of the differential diagnosis. Sleep studies can be relevant, although a thorough history is essential before any laboratory studies. Options beyond treatment of the general medical condition are limited—benzodiazepines and related drugs may be helpful but can complicate the associated medical condition (e.g., decrease respiratory drive). Melatonin agonists (e.g., ramelteon) may have a role. Obstructive sleep apnea should prompt consideration of ventilatory support.

3.7. Catatonic Disorder Caused by a General Medical Condition

Catatonia is a relatively rare psychiatric condition characterized by immobility, extreme negativism or mutism, peculiarities of movement such as posturing, and echolalia (senseless repetition of words or phrases) or echopraxia (repetitive imitation of movement) (1). Sometimes patients show excessive purposeless activity. Catatonia is a serious problem that can become complicated by various concomitant conditions (infections such as pneumonia and urinary tract infection, deep venous thrombosis, and pulmonary embolism) and death. Kahlbaum described an association with medical conditions in the 19th century, although the syndrome is more frequently associated with mood disorders (both mania and depression) and schizophrenia. Encephalitides, head trauma, stroke, CNS neoplasms, seizure disorders, and metabolic conditions such as hypercalcemia and diabetic ketoacidosis have all been associated with catatonia (69). Porphyria is a rare condition that can be associated with catatonia. It is unclear to what extent catatonia caused by a general medical condition is associated with delirium, but this syndrome is clearly part of the differential. A plausible connection between the symptoms of catatonia and the various disorders associated with catatonia is psychosis. Unfortunately, treatment of psychosis with antipsychotics can produce a syndrome, neuroleptic malignant syndrome, that is very similar to or a variant of catatonia. Other drugs associated with catatonia include corticosteroids, disulfiram (rarely used in the treatment of alcohol problems) and illegally used phencyclidine. Benzodiazepines and electroconvulsive therapy (ECT) can be effective treatments of catatonia.

3.8. Personality Disorder Caused by a General Medical Condition

Multiple specific subtypes include labile, disinhibited, aggressive, apathetic, and paranoid types (1). Other than paranoid type, these show little relationship to personality disorders defined elsewhere in DSM-IV-TR. Personality changes caused by a medical condition can be particularly vexing, rather as is the situation when similar problems arise in the context of mental retardation or dementia. Irreversible pathology related to CNS conditions such as TBI (especially involving the frontal lobes), stroke (involving the right side of the brain and with concomitant findings such as unilateral neglect), seizures, and encephalitis seem likely to contribute to chronicity and poor treatment response (32). Substances such as alcohol can cause personality changes. More generally, cognitive, psychotic, mood, and anxiety disorders caused by a general medical condition or the parallel psychiatric disorders should be given consideration and, if present, precedence. Systematic behavioral interventions can be helpful for the personality changes but may be difficult to implement, particularly for infrequent worsening, and difficult to sustain. Caregiver education, patient redirection, and, in some cases, institutionalization, are weak but necessary interventions. A host of medications (antipsychotics, anticonvulsants, lithium, buspirone, antidepressants, sedative–hypnotic drugs, and β blockers to name at least some) have been used with little certainty of benefit. Pharmacotherapy should typically be reserved for urgent and emergent situations, to protect the patient and others from harm.

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3
The Amnestic Syndrome

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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 provides a 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 · Mild cognitive impairment · Transient global amnesia · Wernicke–Korsakoff syndrome

1. Introduction

1.1. History

This chapter focuses 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 because 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 very striking, e.g., the patient's indifference to their deficit, although these features are secondary in prominence to the overwhelming deficits in memory. There is some disagreement regarding 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, although some loss of remote memories is usual. Older memories tend to be protected and resistant to damage. Ribot's first law articulated by the French psychologist, Theodule 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 previous experiences. Amnestic disorders are primarily disorders of anterograde memory, although some component of retrograde memory loss is invariably present. Some (2) have argued that the retrograde impairment is very prominent, although detection of this deficit requires a more specialized approach to cognitive testing.

Memory disorders can be classified based on phenomenology, on etiology, and on nosology. Nosology, e.g., the *Diagnostic and Statistical Manual* (DSM) or International Classification of Diseases (ICD) codes in their various iterations, is the least informative. The most recent DSM, the 4th edition, text revision (DSM-IV-TR), provides only four possible categories based on whether an etiology is known or not:

1. Amnestic disorder caused by a cerebral or systemic medical condition
2. Substance-induced amnestic disorder
3. Amnestic disorder caused by an unknown etiology
4. Amnestic disorder not otherwise specified

Phenomenology is a more useful approach to describing memory disorders.

1.2. Phenomenology of Memory

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

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1.2.1. Types of Memory

1.2.1.1. Temporal

The terms used to describe memory can be very 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, hours, or days earlier. Memory is most often defined temporally, as in immediate, short term, or long term, or by its content.

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.

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

1.2.1.2. Content

Content definitions of memory distinguish between declarative memories, which require a conscious effort (e.g., what is the capital of Idaho?), and nondeclarative memories, which rely on 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. Explicit memory is sometimes known as 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. Edouard Claparede (1873–1940), the French neurologist, provided an early description of a patient who illustrates the distinction between implicit and explicit memory. Claperede's patient suffered from a classic 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 birth date. She was able, however, to learn her way around the facility and to find her room from the dining room and other public areas. This demonstrates intact visuospatial learning. Claperede's famous experiment (which would not be approved by a contemporary institutional review board [IRB]!) involved introducing himself to the patient with a handshake that disguised a sharp pin in his hand. After a short lapse in time, Claperede 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 nonconscious recollection of motor activities and skills. The motor skills of driving a car or hitting a golf ball rely on 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 very good although 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 patient's golf game.

2. Anatomy of Memory

2.1. Diencephalic Versus 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 1930s, however, when cases of Wernicke's encephalopathy were described in nonalcoholic patients with gastric malabsorption, was it appreciated that the etiology was related to nutritional deficiency, namely insufficient thiamine or vitamin B1. Damage to the diencephalon, meaning mamillary 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 such as 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. His seizures were indeed relieved, but he was left with a profound deficit in new learning, with his other intellectual facilities largely remaining intact (3). In a landmark series of studies of H.M., the integral role of the hippocampi in formation of new memories was clearly demonstrated.

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 in section 1.1, is a failure in new learning or in the encoding of new information or the laying down of new memories. 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. The structures most commonly involved are the hippocampus and/or the diencephalon, because 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). The diencephalon includes the mamillary bodies, mamillothalamic tracts, medial dorsal thalamic nuclei, and the internal medullary lamina. Although 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 yet been determined. Some have suggested that the mamillary 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 nonverbal 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 on the memory link of the burning smell with fire that resides in olfactory heteromodal cortex, whereas 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 in section 1.2.1.2, 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 parietooccipital regions or procedural memories in the motor cortex. These memories are distributed in both primary sensory and heteromodal areas.

3. 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 also the ability to consciously recall this information as needed. **Retrograde** amnesia is also usually present, although 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, although 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, although of limited use

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

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 disorders 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 because they use structures other than the hippocampi and diencephalon; as such, the amnestic patient can still learn through priming, conditioning, and other implicit means, although the usefulness of such learning, in the absence of an ability to consciously recall, is limited.

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 amnesia) 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 (TGA), or they may be very prominent, as in the Wernicke–Korsakoff syndrome. In the acute presentation of Wernicke's encephalopathy, there is striking ophthalmoplegia and gait disturbance. Even after timely treatment with parenteral vitamins, there can be residual extraocular 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.

4. Amnestic Syndromes

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 (4). Carl Wernicke, the German neuropsychiatrist, was simultaneously describing a condition also seen in chronic alcoholics that presented acutely with ophthalmoplegia, 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 (5). However, it was not until the 1930s that 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 diencephalic degeneration as the hallmark neuropathological feature (6, 7). They advocated a unitary term, Wernicke–Korsakoff syndrome, which remains in widespread use, although 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 very 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.

4.2. Transient Global Amnesia

TGA, first described in 1964, is characterized by a sudden inability to record new memories in a previously nondemented patient (8). 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, although some advance a vascular spasm hypothesis akin to migraines as a mechanism (9). Others have proposed cerebral venous insufficiency, seizures, and transient arterial ischemia as possible etiologies, although none of these occur regularly in studied patients with TGA and do not, as yet, adequately explain the symptomatic specificity of the syndrome (10, 11).

4.3. Mild Cognitive Impairment

Mild cognitive impairment (MCI) 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.
- Essentially normal activities of daily living.
- Absence of dementia.

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

Ten to 20% of those older than the age of 70 years have MCI. Of those diagnosed with MCI, 10 to 15% will progress to an Alzheimer's disease diagnosis in each year after identification of MCI, such that, at 3 years after diagnosis with MCI, half will have frank Alzheimer's disease. What emerges is that MCI can serve as a pre-Alzheimer's disease diagnosis, although it can also be the precursor state for other dementias. In addition, there are patients who do not progress or even those who improve. MCI diagnostic criteria will collect a clinically heterogeneous population (12, 13).

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 during 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 nonchronological 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, although 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 (14, 15).

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 TGA. Common to all of these provocative etiologies is the relatively focal involvement of the limbic or diencephalic circuitry that subserves new learning or "short-term memory."

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 caused by 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 postperfusion 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 more

TABLE 3.1. Common etiologies for the amnestic syndrome.

Acute onset	Insidious onset
Transient global amnesia (TGA)	Korsakoff's dementia/psychosis
Traumatic brain injury	Other vitamin deficiencies caused by malabsorption, persistent vomiting, malnutrition
Wernicke's encephalopathy	Postherpetic encephalopathy
Anoxic encephalopathy as seen after 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	

than 40% of patients in this series had a performance decline of 20% or more from presurgery testing (16). However, large retrospective studies of dementia patients have found they were no more likely to have had cardiac surgery previously than a nondementia patient control sample. If postperfusion syndrome is a true phenomenon, then it is a subtle change in cognition rather than a full dementia. It is not progressive, because the deficits are related to the insults associated with surgery, presumably microemboli, and further decline would not be expected (17, 18).

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 caused by destruction of mesial temporal structures. General cognition is largely intact.

6. Evaluation

The evaluation of an amnestic patient often takes place in an emergency room or inpatient hospital ward because the deficits may be screaming for attention. The single most important aspect on initial evaluation is determining whether the patient is presenting with an acute Wernicke's encephalopathy. Extraocular movements and gait must be assessed, and there should be a low threshold 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 seem normal because 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 (although 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 patient 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 because general cognition and calculating skills are spared) the words will be lost without trace. No hints or cues will bring theses words back, because 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 do not 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 electroencephalogram (EEG) results reflect this disturbance in sensorium with a diffusely slow background rhythm. In amnestic disorders, the EEG results are 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.

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. TGA resolves spontaneously, although 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 posthypnotic 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 postherpetic 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 use here, because amnestic patients can learn through implicit means, such as conditioning and priming, and still have access to procedural and more remote

("overlearned") semantic memories. However, all of these approaches are confounded by the impairment in conscious recall: i.e., even if the amnestic patient can learn associative mnemonics, if he cannot learn that he knows these mnemonics, they will never be called into play in a given situation in which 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 whether he was to build a house or a rocking chair. A job coach can act as an external conscious memory, although this is rarely feasible for extended periods.

Attempts to supplement a failed conscious recollection through the use of technological supports, such as smart phones, electronic organizers, or personal robotics is 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

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Abstract This chapter records the historical significance of the disorder, mania, which dates back to antiquity. It shows the development of the concept of bipolarity and the more recent broadening of the concept. It starts with the *Diagnostic and Statistical Manual*, 4th edition (DSM-IV) definitions of the disorder, is followed by etiologic considerations, which emphasize the genetic component, then its epidemiology, risk factors, clinical picture, course, complications, differential diagnosis, and treatment.

In this revision of the DSM, the major changes emphasize the much broader concept of bipolar II disorder and a discussion of how these changes will ultimately lead in new directions for understanding the etiology and treatment of the disorder. It is written with an understanding that DSM-V will most likely change the definitions of this aspect of the disorder. Although we have a separate chapter on treatment, as a practicing psychiatrist, this chapter stresses the importance of the use of lithium first, the maximization in maintenance of the dose of whatever medication is used, and the addition of lamotrigine to the treatment armamentarium.

Keywords Bipolar I · Bipolar II · Children · Chronicity · Depression · Hypomania · Lithium · Mania · Rapid-cycling · Recurring illness · Seasonal affective disorder · Secondary mania · Suicide

The affective disorders are disorders of mood. In the past, numerous terms, usually dichotomous, have been used to distinguish these disorders. One major separation made based on genetic and clinical differences that seemed viable was the separation into unipolar disorder and bipolar mood disorders. *Unipolar mood disorder* refers to patients who have depression only. *Bipolar mood disorder* refers to patients who have episodes of both mania or hypomania and depression or episodes of mania only. At this printing, hypomania without depression is not considered a diagnosable disorder (1).

Mania is derived from a Greek word meaning "to be mad." Hippocrates is credited with introducing psychiatric diagnoses into medical nomenclature. Two of the six diagnoses that he proposed were mania and melancholia. 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, 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 seemed to have been used primarily for an illness with an acute onset and with a mood of merriment or rage or fury (2).

In 1686, Bonet used the term *manico-melancolicus* to characterize such patients. In the 1850s, Falret adopted the term *circular insanity*, and Baillarger used *double-form insanity* for similar patients (3). In 1874, Kahlbaum (4) referred to these 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.

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 recognition of mania and the occurrence of mania were apparent to clinicians throughout history.

Schou (6) maintained that Lange (7) first suggested the separation of unipolar from bipolar illness. He and coworkers (8) noted that "periodical depression has no manic phases and differs from manic–depressive psychoses with regard to heredity as well as distribution of somatic types

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and prognosis." They added that manic–depressive patients were more likely chronic and disabled in contradistinction to periodic depressive patients, who were more likely to be discharged and recovered. Leonhard (9), Perris (10), and Angst (11) solidified this point of view. The first American researchers to place emphasis on this distinction were Winokur and Clayton (12). Although bipolar illness was separated from unipolar illness based on differences in age of onset, course, family history, and response to treatment, this separation may not, in the end, prove valid. This author thinks that data are beginning to accumulate that suggest, as Kraepelin (3) 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. (13) and Akiskal and Benazzi (14).

1. Definition

Manic–depressive disease, or *manic–depressive illness*, is the old term in the *Diagnostic and Statistical Manual of Mental Disorders*, *4th edition* (DSM-IV) for *Bipolar Disorders*, which includes patients with mania or hypomania and depression, or mania only. Bipolar I includes episodes of mania (or mixed mania) and depression or mania alone. Bipolar II refers to patients with episodes of depression and hypomania. Cyclothymic disorder is characterized by at least 2 years of numerous episodes of hypomania and depressive symptoms. Bipolar not otherwise specified is the catch-all term for all other patients who may be bipolar but do not meet any of the above criteria.

With bipolar I, each episode is classified as mixed, manic, or depressed. DSM-IV lists the following symptoms for a diagnosis of mania: a distinct elevated, expansive, or irritable mood and three of the following symptoms (four if the mood is only irritable): 1) inflated self-esteem or grandiosity, 2) decreased need for sleep, 3) more talkative than usual or pressure to keep talking, 4) flight of ideas or subjective experience that thoughts are racing, 5) distractibility, 6) increase in goal-directed activity or psychomotor retardation, and 7) excessive involvement in pleasurable activities that have a high potential for painful consequences, plus marked social impairment and no organic factor to initiate the disturbance, including all somatic antidepressant treatments. The mood must be elevated for at least 1 week (or less if hospitalization is required). The mood can also be characterized as mixed (meeting full criteria for manic and depressive symptoms). The disorder can present with or without psychotic features. The psychotic features can be further characterized as either mood congruent, with delusions or hallucinations that are consistent with inflated worth, power, and knowledge; or mood incongruent, with delusions and hallucinations that are not consistent with this elevated mood, such as persecutory delusions, thought insertion or delusions of being controlled, and catatonic symptoms, such as stupor, mutism, negativism, and posturing. The depressive episode also has a mood change, distinct features, and a 2-week duration. For either diagnosis, there is no requirement of disability or hospitalization.

Bipolar II disorder requires that the individual have a history of one or more episodes of major depressive disorder and hypomanic episodes. The hypomanic mood can be characterized as elevated, expansive, or irritable, and must be present for at least 4 days. The mood cannot be characterized as mixed. The same manic symptoms are present for a diagnosis of hypomania but there cannot be psychotic symptoms or marked social impairment. Much attention has been paid to this diagnosis, with many suggestions for change in DSM-V. The boundaries are still being determined. There are several reliable rating scales for hypomania (even in relatives!), so that the diagnosis, even in retrospect, can be made more dependably.

2. Etiology

At present, it is evident that genetic factors play a significant role in the etiology of bipolar affective disorder. There are no other data as strong as those in the genetic area, although they are currently of limited predictive value. Although, with the genome map and DNA probes for linkage markers, transmission and linkage to specific chromosomal markers should be evident, to date, no absolutely reproducible group of candidate chromosome regions has be detected. It may be that we need to separate individuals by dimensions, instead of using categories as we now do to divide individuals as affected, unknown, and unaffected.

In addition to the genetic factors, biochemical, neuroendocrine, neurophysiologic, and sleep abnormalities have been reported, but whether these are specific to bipolar affective disorder or overlap with recurrent unipolar disorder findings is questionable. Besides the confusion of always including some not-yet-identified bipolar patients in unipolar studies (at least 25–33%, up to 50%), one must always consider whether the abnormalities described in any particular report occurred during a unipolar or bipolar depression, during a mania, pure or mixed, or in the well state, and under what conditions (on medications, as one example). Because there are few unequivocal findings, a limited discussion of these issues, as well as of animal models or other disease models that mimic mania, follows.

2.1. Genetics

There is no doubt that bipolar affective 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 contribute to the extent of the genetic knowledge

of this illness: 1) family studies of patients with affective disorder, 2) adoption studies, and 3) twin studies.

2.1.1. Family Studies

Family studies were originally anecdotal. Falret's 1854 article on circular insanity noted that by interviewing the parents of patients, he obtained compelling evidence regarding the hereditary disposition in the illness (3). He concluded that circular insanity was very heritable. He could not decide, however, whether it was more heritable than any other type of mental illness, although he was inclined to think so.

Based on studies by Angst and Perris, and his own work, Winokur (15) summarized the literature and reported that, in bipolar I patients, 52% could be expected to have a parent with an affective disorder, 54% could be expected to have two generations of members affected, and 63% could be expected to have an affective illness in the parents or an extended family member. He reported the incidence of mania in the first-degree relatives as between 4 and 10%. Thus, even in bipolar patients, the majority of affected relatives have unipolar depression.

Gershon et al. (16) looked at schizoaffective, bipolar I, bipolar II, and unipolar patients and healthy controls. The authors concluded that the most common disorder in the relatives of all probands was unipolar affective disorder and that, because there was bipolar illness in the relatives of all ill probands, there was probably genetic overlap between types. In the bipolar probands, the morbid risk in parents and offspring for schizoaffective disorder was 1.2%; for bipolar affective disorder, 9.2%; and for unipolar disorder, 12.3%. Similar figures in siblings were 0.8% for schizoaffective disorder, 6.9% for bipolar affective disorder, and 18.1% for unipolar disorder. The healthy individuals had little illness except unipolar affective disorder (5.7% in siblings, parents, and children). The authors also looked at how the number of affected parents related to illness in the adult children. To do this, they combined the schizoaffective, bipolar I and II, and unipolar patients. If one parent was ill, the risk of having an ill child was 27%, compared with 57% if both parents were ill. Among the siblings of probands, the risk was 24% if no parents were ill and 32% if one parent was ill (not significantly different). They found no significant differences in illness in the relatives when the probands and controls were separated by sex and no increase in alcoholism, drug abuse, or sociopathy in the relatives of patients with these affective disorders as compared with controls. Winokur et al. (17) noted the occurrence of compulsive gambling in the fathers and brothers of some bipolar patients, but without control rates, they could not comment further. This interesting association has recently been renewed by Zimmerman et al. (18) who reported that pathologic gamblers had high rates of comorbid bipolar disorders.

Goodwin and Jamison (19) summarized all family studies to date. Although prevalence rates varied, it was still clear that unipolar depression was the most frequent illness in relatives of bipolar probands, usually comparable with its frequency in relatives of unipolar probands, and bipolar disorder appeared more frequently in relatives of unipolar probands than in the controls gathered simultaneously. There seem to be no recent thorough genetic studies to expand or correct these conclusions. Coryell et al. (20) suggested that bipolar II illness is seen in families of bipolar and unipolar depressive probands. On the other hand, Rice et al. (21) reported, in the collaborative study of mood disorders, that all bipolar II probands came from families with bipolar I or bipolar II members. Simpson et al. (22) also reported that bipolar II was the most common disorder in families of patients with bipolar I and bipolar II disorders. Angst et al. (1) found that hypomanic subjects had elevated rates of mania in their families. Benazzi (23) compared family histories of patients with bipolar II with major depressive patients and found that the bipolar II patients had significantly more bipolar I, more bipolar II (50.7%), more major depressive disorder, and more social phobia in first-degree relatives than did unipolar patients. As the field evolves, bipolar II is closely linked to bipolar I but also includes unipolar family members. Perhaps all patients with family histories of mania should be in the spectrum, although the most important issue for all researchers is to use the same family history instrument so that the diagnoses are reliable. This issue is important for all genetic and biologic studies and for treatment decisions. As early as 1992, Blacker and Tsuang (24) also recommended ways to identify in family members potential bipolar patients nested in unipolar groups and how to use this information in linkage analysis.

With the expanded role of bipolar II and better family study instruments, the family study data are changing. And if, as many authors suggest, the definition of hypomania is changed to include overactivity initiated by a mood change which requires shorter or no length to the episode, the genetics will surely change. The conclusion must be that "bipolar-like" or silent bipolar patients are embedded in unipolar disorder.

Originally, Akiskal et al. (25) suggested using cyclothymic and hyperthymic temperament in families as a marker for the bipolar diathesis. Using their criteria, they concluded that one of every three primary depressive patients belongs to the bipolar spectrum (26). Now, using an expanded definition of hypomania, data are accumulating that at least half of major depressive disorder patients should be diagnosed as bipolar, chiefly, bipolar II (27–30). Based on clinical practice and data, this author recommends that psychotic depressive patients, schizoaffective depressive patients with previous hypomania, and treated postpartum depressive patients (depression in the first month) could be considered silent bipolar patients. Other groups who probably are bipolar are severe treated depressive patients younger than 20 years of age and those who have a somatic therapy-induced mania (antidepressant drugs, sleep deprivation, light treatment, electroconvulsive therapy [ECT]). Hopefully, because these precipitants probably only cause mania in an already prone or vulnerable population, this last group exclusion will be dropped in DSM-V.

Studies of *children* (age varies from 6 to 17 years) of bipolar parents have yielded conflicting results. Even the best studies that included children of bipolar patients and control subjects assessed blindly and with strict criteria do not lend themselves to clear interpretation, although, in the most negative study, out of 76 children, there were 3 with mania or hypomania (by National Institute of Mental Health [NIMH] criteria), and all were from families with bipolar patients (31). A nonblinded controlled longitudinal study of high-risk children concluded that offspring of bipolar mothers had higher rates of psychiatric disorders than children of mothers with chronic medical illnesses or healthy mothers, but somewhat lower rates than children of unipolar mothers (32). Children of bipolar mothers had surprisingly high rates of anxiety disorders.

In the Amish study, a well-done study that included two groups of 110 matched controls (healthy parents who were adult siblings of a bipolar patient and healthy parents), 100 children of a bipolar I parent were assessed and blindly rated annually for 7 years (33). Of the 100 children of bipolar adults, 5 developed a mood disorder, 3 with unipolar depression and 2 with bipolar disorder. In rating total symptoms, 38% of the children of bipolar patients compared with 17% of the other children were rated by the clinicians as having a potential for bipolar disorder. Most of those in the control group were from the families with bipolar illness. The symptoms that were significantly more frequent in the children of a bipolar parent were: anxious/worried, attention poor/distractible in school, low energy, excited, hyperalert, mood changes/labile, school role impairment, sensitivity, somatic complaints, and stubborn/determined. There was also probably a difference in sleep difficulties, but because it was broken down by type, it did not achieve significance. There were additional symptoms that distinguished the two groups of controls, some of which were manic-like in the children of non-affected parents of bipolar siblings. A nonblinded study of children of bipolar patients with no controls also found dysregulation of sleep, instability of self-esteem, and abnormal coping skills (34).

As with the studies of children, studies of assortative mating have produced variable results. Here, too, blind structured assessment of spouses of bipolar patients and controls is essential. In addition, because bipolar studies probably will have equal numbers of male and female spouses and affective disorder rates are always higher in women, the sex of spouses must be controlled for. Merikangas (35) summarized the literature and concluded that there probably was assortative mating in affective disorder (not separated by polarity), but that the magnitude of the problem was unknown. Later, Merikangas et al. (36) indicated that, when assortative mating occurred, it predicted a poorer outcome at follow-up. Waters et al. (37) confirmed an increased prevalence of affective disorders in spouses of bipolar patients, although their interpretation of results was unduly guarded.

2.1.2. Adoption Studies

There is only one study of adoptees with bipolar illness. Mendlewicz and Rainer (38) reported that 31% of biologic parents and 12% of adopted parents of hospitalized bipolar adoptees had an affective disorder. This percentage in biologic parents was comparable with the risk they reported in parents of non-adopted bipolar patients. There are studies of unipolar adoptees and of completed suicide in adoptees that are not specific to bipolar illness.

2.1.3. Twin Studies

Nurnberger and Gershon (39) summarized the twin studies on affective disorders, although not by polarity. The best study that dealt with bipolar illness was that of Bertelsen et al. (40), who reported that, starting with a bipolar twin, the concordance for 55 pairs of monozygotic twins was 0.67, and for 52 pairs of dizygotic twins was 0.20. Concordance was higher in bipolar than in unipolar monozygotic twins. As an extension of that study, Fischer (41) dealt in greater detail with bipolar illness in 28 pairs of monozygotic and 35 pairs of dizygotic twins. When the monozygotic twins were looked at for concordance for affective bipolar only, the concordance was 75% for monozygotic twins compared with 20% for dizygotic twins. However, when other psychosis, severe affective personality disorder, or completed suicide were added as "illnesses," the concordance for monozygotic twins rose to 96% and for dizygotic twins to 49%. Thus, only one pair of monozygotic twins was discordant. Fischer also discussed the issue of discordance in monozygotic twins with one being bipolar and the other being schizophrenic. There were only two pairs from two studies that reported such twins, and Fischer reported these case histories in detail.

To summarize, bipolar affective disorder is a genetic illness. The extent of assortative mating and the extent of illness in children are unclear. Given these clear indications of a genetic role in the diseases' pathogenesis, many genetic linkage studies have been performed without reproducible, clear results (42). One of the most recent studies reported positive linkage at sites 17q24 and 18q12, thus, replicating some, but not other previous findings (43). It is difficult to judge the family interview and history methods, although most of the probands were treated bipolar I patients.

Other genetic researchers suggest that association studies, rather than linkage studies, might be more suitable to identify minor loci, although they need large numbers of patients and controls, but, here too, the results are controversial (44).

It is assumed that, as we clarify the patients and develop innovative techniques and analyses, we will finally make inroads in this obviously genetic illness.

2.2. Biochemical and Neuroendocrine Parameters

The depressant effect of reserpine when administered for hypertension and the euphoric effects of a monoamine oxidase

inhibitor when administered for tuberculosis led to the development of the "biogenic amine hypothesis" for the etiology of depression. The classic amine hypothesis stated that, in depression, there was a functional deficit of either norepinephrine or serotonin at critical synapses in the central nervous system and implied that, conversely, an excess of such amines was associated with mania. Swann et al. (45) reported that the only difference between the manic patients and the control subjects in cerebrospinal fluid monoamine metabolites was an elevated level of 3-methoxy-4-hydroxyphenylglycol (MHPG) in the manic patients, which also had been reported in depressed patients. An unreplicated study by Lewis and McChesney (46,47) presented data showing significantly fewer tritiated [H]imipramine binding sites on platelet membranes in bipolar patients compared with controls, and differences in depression subtypes. It is evident that the third biogenic amine, dopamine, is also important, and that other neurotransmitters or neuromodulators, such as the cholinergic system, the γ-aminobutyric acid (GABA)-ergic system, and the endorphin system, may be implicated in bipolar disorder. Janowsky et al. (48) 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, there is reference to the use of pilocarpine to treat mania (49). Petty and Sherman (50), in a review, indicate a state of confusion concerning the role of GABA in bipolar illness.

In summary, there is no consistent body of evidence to date to confirm that the two poles of illness (mania and depression) are biologic opposites of each other. Clinically, many mixed states have not been dealt with from a putative biologic standpoint.

The fact that *all* antidepressant treatments (accepted antidepressants, novel drugs such as *S*-adenosylmethionine (51,52), ECT, light therapy, and sleep deprivation) seem to precipitate mania has led investigators to expand postulations beyond neurotransmitters to membrane fluidity and functioning of ion channels and second messenger systems. Dr. Winokur liked to remind us that not all studies support the idea that antidepressants precipitate manias in bipolar patients (104, 280–283). Most of the studies supporting the concept of a precipitation are individual case reports or series of patients without controls. Bipolar illness is a highly episodic illness, and it would be reasonable to expect that mania after antidepressant therapy simply is a reflection of the natural history of bipolar illness.

One line of research is to study inositol incorporation (53) into phosphoinositides in cells from bipolar patients (treatment status not given). It was found to be less than in control cells. Kato et al. (54) showed a brain increase in inositol-1-phosphate in lithium-treated bipolar patients. A different approach is to examine the involvement of G proteins in the pathogenesis of bipolar disorder. This approach is particularly convincing because it explains the difference between depression and mania by involving first one and then a second system. Untreated manic patients were found to have hyperactive functions of G proteins. Antibipolar treatments attenuated both receptor-coupled G_s and non-G_s protein function, whereas antidepressant treatment inhibited only G protein function (55,56).

Another line of research that seems worthwhile because it may be relevant to the effects of mood stabilizers such as lithium is the finding that oxidative stress may play a role in the pathophysiology of bipolar disorder. In a study that investigated this in currently untreated manic monozygotic twins found that the twins had higher serum thiobarbituric acid-reactive substances (TBARS) and superoxide dismutase (SOD), which are considered measures of oxidative stress and DNA damage that reversed in one twin when treated but not in the untreated twin (57).

In the same way, 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 (17). Capitalizing on the endocrine challenge test for the diagnosis of Cushing's disease, Carroll et al. (58) began systematically to evaluate the dexamethasone suppression test in depressed patients. They reported that approximately 40% of depressed melancholic inpatients and outpatients given 1 mg dexamethasone at 11:00 P.M. failed to suppress cortisol at either 4:00 or 11:00 P.M. the next day. In most of the studies, the results from the bipolar and the unipolar depressed patients were similar, and manic patients were suppressors. Controversy regarding this test, owing to many difficulties, emerged. Stokes et al. (59), for instance, using data from the collaborative study of the psychobiology of affective disorders, showed that patients in the manic state had the highest percentage of nonsuppression. This was not confirmed by Joyce et al. (60), although they attributed the marked differences to individual variations and failure to assess or report dysphoria during mania. Use of this test by clinicians as a biologic marker for primary depression has been questioned, but everyone agrees that a significant minority of bipolar and unipolar depressed patients have elevated corticosteroid levels, that some (not necessarily the same) are nonsuppressors after dexamethasone, and that in these patients, with recovery, the test results return to normal. A recent study (61) of remitted bipolar patients and offspring of bipolar parents reaffirmed that salivary cortisol levels are normal throughout the day. What happens during the manic state needs further clarification.

Because the neuroendocrine system is related to the amine and immune systems, attempts to integrate findings emerged. Noting a relationship between serotonin activity and production of anterior pituitary hormones, Meltzer et al. (62) reported that serotonin activity in platelets in unipolar, bipolar, and schizoaffective depressed inpatients was significantly decreased but varied independently of those patients who

were dexamethasone nonsuppressors. These findings have not been replicated. Goodwin and Jamison (19) offer a complete discussion of all these controversial parameters. Suffice it to say, the central defect of bipolar illness is yet to be identified.

Another interesting avenue of research is emerging from the study of seasonal affective disorder (SAD). Thompson et al. (63) reported that both bipolar and unipolar SAD patients compared with control subjects displayed an abnormal seasonal variation in the suppression of melatonin by light. There was excessive sensitivity to bright light in the winter (less production of melatonin) and less than normal sensitivity in the summer (it is interesting that bipolar patients may be less likely to use sunglasses than most people). The authors postulated that this change may be caused by a serotonergic input to the suprachiasmatic nucleus. The psychoactive components of melatonin are unclear (64). Lithium affects foveal dark adaptation, perhaps through G proteins (65), but how this all is related remains to be elucidated.

In conclusion, these studies indicate abnormalities and variability in biochemical, neuroendocrine, and second messenger system function, but they do not shed bright light on a specific neurobiology of bipolar illness, either mania or depression.

2.3. Sleep and Other Electrophysiologic Parameters

The sleep parameters of depressed patients are well known. Both unipolar and bipolar depressed patients have shortened rapid eye movement (REM) latency, higher REM density, and problems with sleep continuity (66). Giles et al. (67) confirmed this and added that results from bipolar II depressed patients are similar. Hudson et al. (68) reported exactly the same findings in nine unmedicated manic patients. Sitaram (69) reported that, in remitted, mainly bipolar, depressed patients, arecoline (an acetylcholine agonist) induced REM sleep significantly more rapidly than in healthy control subjects. Some of the remitted patients and healthy control subjects also had an amphetamine challenge test. There was a negative correlation between arecolinergic REM induction and amphetamine-induced behavioral excitation. That is, those former patients who had REM induction sooner also were less likely to develop an elation or excitation with intravenous amphetamines, again suggesting a reciprocal relationship between the cholinergic and catecholamine systems, even in the well state.

In depressed patients who received total sleep deprivation as treatment, 25% of nonbipolar and 30% of bipolar depressive patients became hypomanic or manic (70). Maybe today we would consider all of these patients bipolar. Although these authors advanced several hypotheses that may account for this, they proposed that, during sleep, a substance is produced that is associated with depressed mood, and this is metabolized or stored during wakefulness. It explains the reported response of depressive patients to napping and the diurnal variation of depression. Although the authors do not address it, they must assume that the well-described sleep morphology of depression still allows for or enhances the production of this substance. How this substance relates to induction of mania is also not clarified. The precipitation of mania after a stressful life event (71) could be through sleep deprivation (72).

Studies have shown that between 17 and 45% of bipolar patients have abnormal electroencephalogram (EEG) results (73). Dewan et al. (74) also reported an increase in third ventricular size in remitted bipolar patients compared with control subjects. They found no correlation between this and any clinical, neurophysiologic, or neuropsychometric measures. Brambilla et al. (75) reported an enlarged left amygdala in remitted and depressed bipolar patients, some of whom were drug free and others of whom were taking lithium. Using positron emission tomography (PET), Baxter et al. (76) reported that bipolar and unipolar depressive patients had similar lower left dorsal anterolateral prefrontal cortex blood flow compared with healthy control subjects, obsessive–compulsive patients without depression, and bipolar manic patients. Others have reported normal cerebral blood flow in all affective disorder patients (77). Another report on a mixed group of bipolar patients, mainly taking medication and 5 of 11 of whom were psychotic, compared with healthy control subjects, found decreased brain activation using functional magnetic resonance imaging (fMRI) scanning in patients in brain regions associated with executive control (78). A recent study of serotonin transport binding in bipolar depressed unmedicated patients and control subjects, using PET reported elevated serotonin transporter (5-HTT) binding in the cortex and decreased levels in the brainstem, which is similar to findings of studies of unmedicated major depressive patients (79).

Finally, there is continued exploration of the use of magnetic resonance spectroscopy (MRS) to examine alterations in brain neurochemistry of bipolar patients that might be associated with the development of the disorder and the effects of treatment (80).

2.4. Animal Models

Robbins and Sahakian (81) reviewed the animal models for mania, including a thoughtful discussion of how to relate clinical symptoms to animal behavior, criteria for the ideal animal model of a syndrome, and a discussion of models produced by drugs, lesions, and behavioral manipulations. Their own research emphasized the amphetamine-induced model and is particularly interesting in light of the clinical studies of amphetamine-induced symptoms and syndromes in humans. Unfortunately, even in 2007, researchers would agree that we still lack an animal model for mania (JR Calabrese, personal communication, 2006). Fawcett et al. (82) reiterate that there are no good animal models for mania.

2.5. Secondary Mania

Krauthammer and Klerman (83) thoroughly reviewed the literature on secondary mania. They required specific criteria to include cases as mania. The major reported causes have been neurologic conditions such as neoplasm, epilepsy, head injury, cerebrovascular lesions, drugs, metabolic or endocrine disturbances, infections, or other systemic conditions. Winokur, in the last edition of the current book, suggested that perhaps a better term than secondary mania might be *induced mania. Secondary mania* implies only that a mania occurs in relation to a temporal sequence. The Krauthammer and Klerman (83) paper presents a series of organic and neurologic factors that precede the mania, suggesting that some kind of abnormal metabolism, tumor, or other biologic disturbance caused the mania.

Other articles (84–86) have commented on the development of mania after a closed head injury. Some suggest that the intervening variable in head injury is seizures; others fail to confirm this. Mania developing after specific left and right intercerebral pathology (87) also has been reported in the literature.

Several reviews summarized the differences between organic and non-organic mania (88–90). Patients with induced mania are frequently older at their age of onset, their mood is more typically irritable rather than manic, they are less frequently psychotic, their family histories are more frequently negative, and they do not respond to the usual treatment but do well on anticonvulsants.

Another set of recent articles reviewed this concept and confirmed many, but not all of the differences above (91). These researchers compared primary mania with HIV-induced secondary mania in Uganda. The patients with secondary mania were older, more cognitively impaired, irritable rather than happy or euphoric, had more aggressive or disruptive behavior, and had higher rates of paranoid delusions and visual and auditory hallucinations. In a thoughtful commentary, Robinson (92) reminds us that many of the findings could be related to HIV status rather than secondary mania, but also emphasizes that, with late-onset mania, one should always exclude organic causes. Equally as interesting, however, is that he states that, in many published cases, the patients seem to have more than one contributory factor (known as the two-hit hypothesis). This may explain why it has been relatively rarely reported. However, with the recent wars, closed head injuries are common, thus, between the AIDS epidemic and the head injuries, effective treatments should be tested.

There is also a set of reports on the occurrence of bipolar illness in patients with mental retardation (93–95).

Besides the mania that may be precipitated by somatic therapies for depression, mania also has been reported during treatment with corticosteroids, cocaine, and L-dopa, as well as during the spontaneous use of amphetamines and khat, a leaf used as part of the culture of people of North and South Yemen. Tatetsu (96, 97) reported on 131 Japanese patients who, because it was legal and available, used methamphetamine after World War II. The most common diagnoses in both the acute and stationary stages in these addicted patients (30 to 90 mg/day administered intravenously) were either manic–depressive illness or manic–depressive illness with schizophrenia-like features. The paranoid delusions that developed were compatible with a diagnosis of manic–depressive illness. Gough and Cookson (98) reported that, after the use of khat, a patient became manic with elation, hyperactivity, pressured speech, diminished appetite, poor sleep, and delusions. The patient's disorder was called *schizophreniform.* The drug screen was positive for amphetamines but negative for other drugs. Another report described a patient given baclofen, which is structurally related to GABA and presumably acts as a GABA agonist or as an inhibitor of substance P, for cervical myelopathy who developed a manic-like syndrome 1 day after he discontinued the drug (99). Numerous other drugs and drug withdrawals are reported to be associated with the onset of mania. These should be considered secondary manias and treated as such, although the long-term course (e.g., recurrences without the drug) may prove the illness to be bipolar disorder.

As with the neurobiology and electrophysiologic findings, these animal and human models provide evidence that this illness is a biologic brain disorder but emphasize the complexity, diffuseness, and variability of the syndrome rather than clarify the cause.

3. Epidemiology

Because of the inclusion of bipolar II and the expansion of the bipolar spectrum, estimates of prevalence have increased since the rates reported by Boyd and Weissman (100) and the epidemiologic catchment area (ECA) studies (101). Lifetime prevalence rates for DSM-IV bipolar I and II disorders from the National Comorbidity Survey Replication were 3.9% (102). Prevalence rates for the bipolar disorders differed significantly by age, with the youngest having the highest rates. The 12-month prevalence rate was 2.6% (103). Although prevalence rates for schizophrenia were not measured in these studies, bipolar disorder clearly is a more common illness than schizophrenia. These prevalence rates do not include all the "softer" cases and the depressive patients who have not yet switched. Many authors contend that major depression and bipolar disorders should be approximately equal in prevalence, mainly because of the bipolar II patients embedded in the major depressive disorder group (104, 105). In all of these studies, the distribution of male to female patients was approximately equal in bipolar I but 2-to-1, female-to-male patients, in bipolar II disorder.

Although there are conflicting reports (106), most researchers agree that the majority of patients, particularly women, begin with depressive episodes (107–110).

In a long-term prospective study of hospitalized mood disorder patients, Angst and colleagues (111) reported that

depressed patients converted to bipolar I at a rate of 1% per year and to bipolar II at a rate of 0.5% per year. More than half of their severe mood disorder patients became bipolar. However, this conversion rate is less for outpatients with depression. Akiskal et al. (112), in a younger sample, reported that 20% of 206 depressed outpatients switched to bipolar I or II disorder an average of 6.4 years after the initial identification. If the illness began at a younger age, the switch was earlier. Krauthammer and Klerman (113) estimated a similar switch rate. Finally, in a blind systematic assessment in a 7- year follow-up of 500 outpatients with the whole spectrum of DSM-IV diagnoses, 3.2% of the patients converted to bipolar disorder, chiefly bipolar I (114). The rates of conversion were approximately the same for those who had major depression, questionable depression, secondary depression (to another major psychiatric disorder), or another psychiatric diagnosis. Factors besides young age found to be associated with a change of polarity from unipolar to bipolar were hypersomnic and retarded phenomenology, psychotic depression, and postpartum episodes (115). In addition, a large percentage of young male patients who were depressed switched (115). A family history of bipolarity and a pharmacologic hypomania produced by antidepressants also were predictive of a bipolar outcome. The mean age at which the switch occurred was 32 years. The average number of previous episodes was two to four. To summarize, these reports contain huge differences in switch rates (from 3 to 50%), which probably reflect first the severity of the initial depression, the length of follow-up, and the expanding definitions of bipolar II disorder. Only follow-up data collected blind to entry conditions in a group of patients with many disorders would give us the correct answer.

No data suggest that unipolar mania differs from bipolar mania. Unipolar mania was said to be rare and to constitute only 2 to 5% of all of the patients in this category. In the Jorvi Bipolar Study (JoBS), only 4.4% of these recently diagnosed inpatients and outpatients reported having mania only (110). Nurnberger et al. (116) reported that 16% of a group of bipolar patients had never been hospitalized or treated for depression, and Abrams et al. (117) reported that 18% of patients hospitalized for affective disorder (not necessarily bipolar) were unipolar manic patients. Interestingly, Kraepelin (5) originally reported that 17% of his 900 manic–depressive patients were exclusively manic. Excluding the outliers, the range is from 5 to 18%. Some feel that the longer or the more closely a patient is followed, the more likely it will be that depression is recognized.

4. Risk Factors

The onset is usually from the teens to the 50s, with the average age of onset being 30 years. More than one third of bipolar illnesses begin in the teenage years (17). Numerous studies have indicated that, in the teenage years, bipolar illness can be mistakenly called schizophrenia, antisocial personality, or borderline personality disorder. Actually, there should be more adolescents diagnosed as bipolar (either manic or depressive) than as schizophrenic. Akiskal (118) indicated that the clinical presentation of adolescents with bipolar disorders, in decreasing frequency, are "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. Although the last was extremely uncommon, it can occur. A recent review discusses the diagnostic issues (119), and the reader should refer to Egeland et al. (33) for the symptom list in the at-risk children.

The literature on late-onset (older than 50 years of age) bipolar illness is confusing because some of the patients discussed had episodes of depression before the age of 50 years but did not become manic until older than the age of 50 years. A study of manic episodes in older people indicated that a mean of 10 years elapsed between the first depressive episode and the first manic episode (120). Still, there are onsets after age 50 years that are not associated with organic pathology (121–124). Because this age group is enlarging, we should see more instances.

There are no racial differences in the incidence or prevalence of bipolar illness. A fair amount of literature indicates that both Hispanic and black patients have high rates of bipolar affective disorder when inpatients are studied, and that it is frequently misdiagnosed as schizophrenia (125–127). In the ECA study (101), there were no differences in the lifetime prevalence of mania by race, and, in fact, in the St. Louis data, there seemed to be an excess of mania in the black patients. In the same data set, mania was equally prevalent in urban or rural residents but was significantly more prevalent in noncollege graduates than in college graduates. These race and education findings may be related.

Interestingly enough, there is little comment on the marital status of bipolar patients. In the collaborative study, there were significantly more single bipolar patients than single unipolar patients, a fact also mentioned in the reports on race and bipolar illness. A young age at onset probably correlates with being single.

A positive association between bipolar affective disorder and high socioeconomic status was noted previously (128) but not confirmed in the ECA study (101). Coryell et al. (129) reported significantly higher socioeconomic status in only the relatives of bipolar patients. The data on immigration status of bipolar patients are controversial.

A well-done study by Ambelas (71) confirmed what clinicians suspected: there is a strong correlation between stressful life events and first manic admissions, which lessens as the illness progresses. This is particularly true for younger bipolar patients and is significantly linked to mania and not depression. Studies of bereavement have shown that the most common somatic symptom after this stress is insomnia (130), and this, coupled with data from sleep-deprivation studies, has

caused researchers to posit sleep reduction as a final common pathway to mania (131). Knowledge regarding the association between stressful life events and insomnia is essential in managing bipolar patients.

All studies have confirmed the postpartum period as a risk period for mania in known bipolar patients (17, 132), patients with serious previous depression (112), and probably those with a bipolar diathesis (133).

Periodicity of this illness is true for some patients, with fall/winter depression and spring/summer mania being most frequently described. Sayer et al. (134) confirmed in the southern hemisphere what had been reported in the northern hemisphere (135), that hospital admissions for mania have a spring/summer peak. Onset of illness should be recorded for each episode to highlight patterns of illness. More recently, the seasonality of the mood disorders has been emphasized, leading to the classification of SAD (136,137). Large numbers of SAD patients are bipolar. Depending on the number of bipolar II patients included, percentages vary from 8 to 100% (19), with most studies recording more than 50% as bipolar spectrum. A community sample study with control subjects confirmed that bipolar patients experience greater seasonality than those with depression or healthy control subjects (138). This has important implications for the management of these patients.

The personality traits of bipolar patients may be unremarkable. Akiskal et al. (139) identified 46 outpatients (2.3% of the outpatient population) as cyclothymic and reported that 22% became bipolar in the follow-up period. This seems reminiscent of the earlier discussion of early childhood symptoms. Some researchers indicated that, even in remission, manic patients evaluate themselves in a positive way (140–142). Others emphasized the achievement-oriented personality of the bipolar patients (143, 144). Still others have found that bipolar patients who are well or stabilized on lithium have personalities similar to those of control subjects (145, 146). Bech et al. (147) suggested that lithium mutes the cyclothymia and causes bipolar patients to have test results more similar to unipolar patients. 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 nearly normal whereas bipolar II patients emerged as mood labile, energetic and assertive, yet sensitive and brooding (148). Bipolar I patients tested low on neuroticism and bipolar II patients tested high on neuroticism, mostly because of their mood lability. Angst and Clayton (149) compared premorbid personality traits in young men who developed bipolar illness with those who remained well, and found no differences. Unfortunately, the personality test did not measure obsessionality, the trait Klein and Depue (150) reported may be associated with risk for bipolar disorder in the offspring of bipolar probands. Others report a modest association between borderline personality disorder and bipolar disorders (151). Thus, no personality trait or feature can be identified as a risk factor, and, as yet, no childhood features are predictive of bipolarity. Cyclothymia is probably an early manifestation of the illness rather than a personality trait (143, 152). It seems as likely that personality traits associated with early onset recurrent depression will identify bipolar patients.

5. Clinical Picture

As previously emphasized, the typical bipolar patient starts with an episode of pure depression. Angst (107) reported that the ratio of depression to mania in the first episode was 3:1 for women and 3:2 for men. Still, mania or a mixed manic and depressive state is the hallmark of this illness (17). Pure and mixed states probably occur with equal frequency, although some reports combine mixed and cycling episodes, which elevates the percentage presenting as a mixed state (153–157). The episodes may be triphasic (depressed, manic, then depressed) but most usually are biphasic (manic then depressed) (17). Mania can begin suddenly with the development of a full-blown syndrome over hours (causing some to posit a substance in the bloodstream), or it may be a more gradual state, developing 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 miss the first indications. Early in the course of illness, mania can be preceded by life events, including bereavement, but, as the illness continues, there are fewer precipitants.

The picture can vary from an excited, talkative, loud, overreactive, somewhat amusing individual, to a completely disorganized, intrusive psychotic individual. The mood is always elated, angry, or irritable. Many patients 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. Racing thoughts, pressured speech, circumstantiality, irrelevancies, and flight of ideas characterize thoughts and language. Decreased need for sleep or insomnia, 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 probably the basis for the symptoms of excessive telephone calls, extravagances, and excessive writing. One or two themes usually predominate. The themes may be religious, political, financial, sexual, or persecutory. All varieties of psychotic symptoms have been reported in the manic patient (158, 159). The best documentation of this is probably the Carlson and Goodwin (160) study on the evolution of a manic episode. At the height of the manic episode, patients exhibited unusual psychomotor activities, incoherent thought processes, and delusions and hallucinations that were

bizarre and idiosyncratic. They found that besides hyperactivity, extreme verbosity, pressure of speech, grandiosity, manipulativeness, irritability, euphoria, labile mood, hypersexuality, and flight of ideas, 75% had delusions that were either of control or sexual, persecutory, or religious; 75% had assaultive or threatening behavior; 70% had distractibility, loose associations, and a fear of dying; 60% were intrusive; 55% had some delusions; 50% had religiosity; 45% used the telephone excessively; 45% had regressive behavior (urinating or defecating inappropriately and exposing themselves); 40% demonstrated symbolization or gesturing; 40% had auditory and visual hallucinations; and 35% were confused. Confusion is a well-documented symptom of acute mania. In a chart review, 58% of 31 manic patients were reported either to be disoriented or to have memory lapses (158). Kraepelin (5) used the term delirious mania.

Andreasen (161, 162) and Andreasen and Powers (163) looked at thought disorder in mania and found that besides being overinclusive, both behaviorally and conceptually, manic patients were tangential and had derailment, incoherence, and illogicality that was equally prominent as in schizophrenic patients. The manic patients were more likely to have pressured speech, distractibility, and circumstantiality. The schizophrenic patients more frequently had poverty of both speech and content of speech. Harrow et al. (164) confirmed and extended this, indicating that, at follow-up, in partial remission, almost half continued to have thought pathology. Brockington et al. (165) reported similar follow-up findings. Catatonic features during a manic episode have been well documented by Abrams and Taylor (166) and reconfirmed by Fein and McGrath (167). Pope and Lipinski's (168) comprehensive article emphasized that between 20 and 50% of well-validated bipolar patients have psychotic symptoms, including hallucinations, delusions, catatonia symptoms, and Schneiderian first-rank symptoms.

Most, but not all, investigators report inconsistent and minimal differences in symptoms in bipolar and unipolar depressive patients (169). One exception may be psychotic depression, especially occurring in people under age 30 years. Delusional depression, by clinical course, outcome, treatment, and family studies, predicted bipolarity in the patient and family members (170). Weissman et al. (171) even reported that children (ages 6 to 23 years) of delusional depressive patients compared with children of nondelusional depressive patients had a threefold increase in cyclothymia, were more often described by health professionals as hyperactive, and had increased school and social impairments. Although not confirmed, perhaps even older-onset delusional depressive patients should be considered part of the bipolar spectrum, especially in deciding treatment, maintenance, and genetic studies.

The other distinctions that some investigators think characterize the depression of bipolar II patients are gain of appetite and weight, hypersomnia, and fatigue (172).

Bipolar depressive patients have high anxiety scores, similar to unipolar patients. Freeman et al. (173, 174) urged us to remember that when treating these patients. They also make more serious suicide attempts during follow-up.

The following case illustrates a bipolar illness with an untreated, unrecognized first episode of depression and psychotic mania.

A 22-year-old single man was referred for consultation. He gave a clear history of episodes of psychosis beginning in May and June at age 17 years, after graduation from high school. He was going with a group to Israel, and in anticipation of this trip, he got excited and experienced insomnia. On the airplane, he developed the idea that his peers were sending messages by some strange visual communication. He thought that their facial expressions told other stories and began to think that he could read their thoughts and minds. He also developed the idea that something was visibly wrong with him and that security guards in Israel noted this. In the midst of this, he lost track of time and became convinced that the group could not go to the Wailing Wall because it was Friday, when indeed it was Wednesday. He refused to leave his room. After that, he included the group leader in his scheme, thinking "they" were trying to fool him and retain him in Israel. He remembered that his thinking was loud and fast and that he was angry. He was hospitalized in Israel and returned to a hospital in the United States.

His second episode occurred in April, 2 years later. In this episode, his psychotic symptoms were grounded in the grandiose delusion to save the world. He began to write a book. He also wrote clever but disjointed letters to the governor that pertained to fighting crime (this was probably originally based on some incident such as an attempted rape in his dorm). He developed the idea that one way to help crime and stabilize the financial market was to construct more jails, so he began to buy stock in construction companies. He believed that he would become famous for this plausible plan. Finally, because of his letter writing, the police decided that he might be dangerous, and he was committed. Again, he remembered being excited, needing no sleep, talking fast, and not eating.

His third episode occurred again in April of the next year and had a similar theme. Each time he was diagnosed as manic and was put on lithium and a major tranquilizer, but he objected to taking lithium continuously. When I saw him, he was taking no medicine. He was depressed, with slowed thinking, difficulty concentrating, and difficulty making decisions. He had intermittently returned to a difficult college and had completed courses but had not completed his degree. He felt discouraged about that and thought that it was useless to go to school or work. He was thin and distraught looking. In retrospect, he stated that he probably was depressed in high school in the spring of his senior year, when his grades fell and he did not do as well on the swimming team and developed a great deal of interpersonal difficulty with his father.

His mother had recurrent bipolar affective disorder, but he has always blamed his father for his illness.

For several years, he was stabilized on lithium and an antidepressant. He graduated from college but found no suitable long-term work. He was fired from a job as a postman before the probation period was up. He was far from well adjusted. He complained that he never smiled. He remained single, lived at home, and was dependent on his family. His goal was to marry and have a reasonable job. He had had numerous long trials of psychotherapy. Because of side effects (alopecia, tremor) and no mania for 7 years, he wanted to stop the lithium and did. Before he did, we discussed the symptoms that we should anticipate if he got manic. He voluntarily listed the following symptoms: racing thoughts, distractibility, grandiosity, driving faster and in more of a hurry, talking faster, excessive buying and long-distance telephone calls, increased humorousness with free associations and punning, playing records louder, listening to music and bothering more people in the household, and becoming evangelistic. He did not think that his sexual interest changed (it was always high) or that he had weight loss or increased energy. After years of managing him on one antidepressant or another, he finally agreed to take a monoamine oxide (MAO) inhibitor. Previously, he had resisted either because he maintained that the treatment might interfere with treatment for an acute asthma attack or because the drugs were dangerous and I was trying to kill him. Within days on an MAO inhibitor (he frequently escalated the dose without approval); he became irritable, humorous, and argumentative. Mania was diagnosed. He stopped the MAO inhibitor but refused treatment. His family also would not intervene. He moved to a motel. He had some care, but not hospitalization. The illness essentially ran its course. He now takes lithium and antidepressants and sees another psychiatrist.

6. Course

Bipolar illness is definitely a recurring illness. In a 6-year follow-up of 42 patients, Bratfos and Haug (175) found that 7% recovered without relapse, 48% had one or more episodes, and 45% had chronic courses. Grof et al. (176) reported that virtually every patient had a recurrence. There are no comparable data from an outpatient clinic, although the treatment studies show high relapses when such patients are put on placebo and, therefore, complement these data.

The clearest data on the characterization of the illness come from an early collaborative European study (176, 177). Patients were treated for their affective episodes and received no prophylactic treatment between episodes. The investigators were particularly interested in documenting numbers of episodes, lengths of episodes, and other details pertaining to episodes. The average manic episode lasted for approximately 3 months, and the average depressive episode lasted for approximately 4 months. The duration of episodes did not change remarkably with increasing numbers of episodes. Initially, with each episode, the interval between the episodes tended to decrease. However, once the patient had gone through a number of episodes, perhaps more than five, the duration of the cycle—defined as the time from the beginning of one episode to the beginning of the next—became stable. Thus, the duration of the time between attacks had a tendency to decrease and the course deteriorated, but it ultimately bottomed out at a cycle every 6 to 9 months. The authors concluded that the most useful way to predict a patient's future course was by his or her past course; e.g., if a patient had three episodes in the past 2 years, the short-term future course would be similar. Calabrese et al. (178) also showed from the treatment studies that the polarity of the index or most current episode predicts the polarity of the relapse into a subsequent episode. Those bipolar patients presenting with depression relapse into depression and those presenting with mania relapse into hypomania, mania, or mixed states. This too then must be considered when choosing a mood stabilizer and when testing them for relapse prevention.

Between 15 and 20% of bipolar patients who present for treatment exhibit rapid cycling. Coryell et al. (179) applied prospectively the usual definition for rapid-cycling patients (four or more episodes of mania, hypomania, or depression in a single year) to the first 52 weeks of an intensive follow-up and compared these patients with nonrapid-cycling bipolar patients. Rapid-cycling patients were more likely to be female patients ($\sim$75% in many studies), but, in every other way, including thyroid status, family history, and long-term treatment outcome, as well as suicide and suicide attempts, they seemed similar to other bipolar patients. Rapid-cycling patients had less previous mania but more cycling, especially with hypomania. After the defined first year, they did less well for the second year, but by the third, fourth, and fifth years, their outcomes were as good as those of other bipolar patients, and there was no relationship between treatment with antidepressants and outcome. Whether or not there is an association between rapid cycling and low-grade hypothyroidism is controversial (180, 181), although, because these may be refractory patients, levothyroxine should be tried.

In summary, numerous studies have shown that if the presentation is manic then dysphoric mania, rapid cycling, and psychosis predict a less favorable 6- and 48-month outcome (153–156, 179, 182–185). If the presentation is depression, rapid cycling predicts a poorer 2-year outcome (153, 186). If the bipolar disorder is complicated by alcoholism or substance abuse, the outcome is also less favorable (187–189). The longer-term outcome may be more favorable.

This is consistent with the interesting and tentative finding from the work of Grof et al. (176) that there may be an extinction of the pattern of episodes after a certain number. The authors found that although the total number of episodes in a lifetime varied from 2 to more than 30 (and 42% of patients had more than 10 episodes), still, the median number was 9 episodes, whether the patient had been studied for 5 or

40 years. The authors interpreted this to mean that although the short-term prognosis of bipolar affective disorder may be poor, the long-term course may be better. Winokur (190) suggested the same thing from a different database. Here, however, the studies on lithium maintenance would speak against this, for they show that even patients up to age 65 years who have recurring bipolar illness relapse if lithium is discontinued. Perhaps lithium blocks the extinction of the illness.

The question of chronicity in bipolar disease is not a moot point. Winokur et al. painted a picture similar to that of Bratfos and Haug (17, 175). In a 2-year follow-up of 28 patients, 14% were well in every way, 46% had additional episodes but were well in between, 29% never achieved more than a partial remission of symptoms, and 11% were chronically ill. Only four patients were in the first episode of the illness, and in these four, one had a partial remission, two had complete remissions with subsequent episodes, and one remained entirely well. Welner et al. (191) 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. In a much referred to analysis of the weekly status of bipolar I and II patients (most who were hospitalized at the beginning of the naturalistic study and were followed for an average of 13 years), Judd et al. (192) reported, as Bratfos and Haug (175) did, that the long-term symptomatic course of bipolar I disorder was chronic, with the predominant symptoms being depressive (as the patient illustrates). A similar course was found for patients with bipolar II disorder (193). Paykel et al. (194), in an 18-month follow-up with in-person assessments every 8 weeks, also reported that subsyndromal residual symptoms are an important problem for bipolar patients. Judd et al. (195) reported that, although subsyndromal depressive symptoms lead to the greatest disability, subsyndromal hypomanic symptoms seemed to enhance functioning in bipolar II patients. Kessing (196), in a record study that investigated the naturalistic longitudinal course of bipolar and unipolar patients, also reported that the rate of relapse did not decline despite the introduction of new treatments. However, in all of these studies, treatment was not controlled.

There are several more favorable outcome studies; one was Petterson's (197) study of a group of patients treated in Sweden. She observed the clinical, social, and genetic aspects of 123 patients for approximately 5 years. At the end of the study, a large number of patients showed work capacity that was more satisfactory and better social adaptation. This was a group treated by a single investigator. It may be that in treating chronically ill patients who require maintenance therapy, psychological skills are an essential ingredient to a more favorable outcome. Miller et al. (198) also reported that their carefully treated patients were asymptomatic 59% of the time in a 23.7-month follow-up. Thus, perhaps with complete and vigorous treatment, the course could be more favorable.

6.1. Complications

The most serious consequence of this illness is suicide. Not dividing patients by polarity, a summary of the relationship between suicide and primary affective disorder showed that the suicide risk among patients with affective disorder was more than 30 times greater than that of the general population (199). Between 10 and 15% of all deaths of patients with affective disorder were accounted for by suicide (200). In bipolar disease, as in unipolar disease, there is a trend for the suicide to occur early in the illness and less frequently as the disease continues, however, there is a continued risk with each new episode.

Angst et al. (201, 202) reported that, in their naturalistic 40 to 44 year follow-up of patients hospitalized for a mood disorder, 10.2% of their bipolar patients died by suicide. In addition, although the more seriously ill patients got treatment, the suicide rate was much reduced in those who were treated compared with those who were untreated. The treatment was with lithium, antidepressants, and antipsychotics, mainly Clozaril.

Follow-up outpatient studies have found lower suicide rates in unipolar and bipolar patients (197, 203, 204). Morrison (205), also in outpatients, found lower rates in unipolar patients but not in bipolar patients. It is essential that treatments be controlled to reach conclusions.

It is also important to emphasize that bipolar patients die by suicide in the depressed phase of their illness. Robins (206) reported from the psychological autopsy study of 134 suicide victims that, although the most frequent diagnosis in these people was a mood disorder, no patient was manic at the time of the suicide (206).

Suicide attempts have been reported to be higher in bipolar patients, especially men (207, 208).

There is also a link between bipolar disorder and excess cardiovascular mortality (209, 210), which may be especially true in inadequately treated bipolar patients (211, 212). This was nicely highlighted by Angst et al. (201), who found that bipolar patients had elevated rates of death from cardiovascular diseases and all vascular diseases; but, here again, the treated, compared with the untreated patients, had significantly higher death rates from all of these illnesses as well as cancers and other causes.

One report (213) showed an increased prevalence of diabetes in hospitalized bipolar patients compared with *all* other hospitalized patients, such as schizophrenic patients, alcoholic patients, and retarded patients. This has been well documented by McIntrye et al. (214) and has become much more evident with the atypical antipsychotics and the metabolic syndrome.

Both Bratfos and Haug (175) and Angst (personal communication) reported that these patients develop dementia at a higher frequency than would be expected compared with appropriate age-matched control subjects, but, without autopsy findings, it is unclear if this is Alzheimer's disease.

In addition, there may be an increased association between heavy drinking and acute mania and between alcoholism and bipolar disorder (215) and substance abuse and bipolar disorder (189, 216).

There is also an association between pathologic gambling and a bipolar diagnosis (217). In the early family study of bipolar patients (17), some family members were pathologic gamblers. In a more recent study of pathologic gamblers (18), it was noted that they had high comorbidity, especially with bipolar disorder. It is not surprising, because both groups of patients are risk takers.

Another factor worth noting is that bipolar disorder costs twice as much in lost productivity as major depressive disorder (218). It is estimated that each US worker with bipolar disorder averaged 65.5 lost workdays in a year compared with 27.2 for major depression.

Some have indicated that bipolar patients' marriages ended in divorce more frequently than those of unipolar patients or appropriate control subjects (219). Even in those marriages not ending in divorce, 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 (141).

Thus, the illness has an impact on marriage, job, child rearing, and all aspects of life. This is clearly recorded from the MEDSTAT Group's MarketScan Health and Productivity Management database (220).

Once more, Petterson (197) reported better social and medical outcomes. In her data, the distribution of marital state and frequency of marriage was largely in agreement with the general population. In several cases, there were divorces that occurred in connection with the patient's illness, but there also were reconciliations that were attributed to lithium treatment.

The bipolar patients she studied had fewer children and more childless marriages than the general Swedish population. The finding of decreased fertility also was reported by Baron et al. (221).

The one reproducible fact, already mentioned, is that bipolar women of child-bearing age are at increased risk for episodes after delivery and, once they have had one, almost all have postpartum episodes after subsequent pregnancies.

With regard to criminality, Petterson's (197) patients had fewer convictions than expected in comparison with the general population, a finding replicated in other studies. An interesting set of studies (222), however, indicates that symptoms of mania are more common in forensic settings than was generally thought. In studying patients admitted to St. Elizabeth's Hospital in Washington, DC, the authors found that 11 of the 13 attempted crimes against the president of the United States, so-called White House cases, were perpetrated by people diagnosed as having an affective disorder, and the majority of them were bipolar disorders.

In summary, although numerous problems can be anticipated with the development of a bipolar affective disorder, there is some hope that maintenance therapy can significantly alter the course of the illness.

7. Differential Diagnosis

As indicated, other disorders have similar symptoms, course, and outcome, including high chronicity and suicide, as well as similar ages of onset, types of onset, and percentage single. Only family history can reliably distinguish the bipolar patient. Remember, symptoms are not absorbed from the patient; they are elicited. Therefore, all symptoms, including mood, should be asked of the patient.

7.1. Schizophrenia

Schizophrenia and mania are alike in many ways. The symptoms of a current episode can be similar in mania and schizophrenia. One symptom is not pathognomonic for either, although the mood of merriment, elation, ecstasy, or even irritability is much more likely to occur in the manic than in the schizophrenic patient, but there are some hypochondriacal or grandiose schizophrenic patients who maintain a haughty, elated affect. Studies of diagnostic criteria for mania (223) indicated that the triad of symptoms—manic mood, rapid or pressured speech, and hyperactivity—is robust, so that perhaps any patient with all three symptoms should be considered manic regardless of number or content of other symptoms. In patients partially treated with lithium or other antimanic 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 mania should be characterized as a change from the person's premorbid self. Schizophrenia should be more insidious, but it, too, can begin with depression *or* anxiety.

The course of the illnesses could 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 patients than in schizophrenic patients. Both have high suicide rates, with 10 to 15% dying by suicide. The most reliable difference in these two illnesses is the family history. Although both are hereditable/familial, at least 50% of manic patients should have some family history of an affective disorder (mania or depression). Studies of schizophrenic patients show a significant but less striking increase in schizophrenia in their families but no increase in affective disorder over the population prevalence of approximately 6 to 8%.

7.2. Paranoid Schizophrenia

After the teenage years, many manic patients are misdiagnosed as paranoid schizophrenic patients. This seems to be particularly true with black and Hispanic patients. Again, the other indications of a manic syndrome, such as previous episodes, mode of onset, and family history, should help to differentiate patients.

7.3. Catatonic Schizophrenia

Because, when looking at catatonic symptoms, patients are more frequently bipolar or manic than any other diagnosis, all patients in whom the diagnosis of catatonic schizophrenia is entertained should be evaluated carefully for depressive and manic symptoms, previous episodes, and family history. Some manic patients become mute when their thoughts go so fast that they cannot speak. A "flat affect" is not uncommon or unusual in a bipolar patient treated with or maintained on antidepressants. The Amytal interview may still be useful in uncovering depressive delusions, disjointed manic thoughts, or disorientation (organicity).

7.4. Schizoaffective

Using the research diagnostic criteria (RDC) definition of schizoaffective, which splits patients into schizoaffective mania and schizoaffective depression, all studies show that the schizoaffective manic patients (224, 225) are similar to manic patients, especially mood-incongruent mania, as defined in DSM-III. They all agree that the schizoaffective manic patient probably has an earlier age of onset and a more malignant course, but the biologic markers and the family history data indicate that they are in the bipolar spectrum. Joyce (226) also concluded that patients with teenage onset have *more* schizophrenic symptoms. Because schizoaffective mania is so much like mania, it probably is better to call all such patients "bipolar manic with mood incongruent features."

On the other hand, schizoaffective depressive patients, who are usually a smaller group, seem to be a conglomerate of many different patients, such as schizophrenic patients, depressive patients, the spectrum of anxiety disorders with secondary depression, and alcoholic patients or drug abusers with secondary depression (227). If schizoaffective manic patients are removed from schizoaffective depressive patients, there are almost no schizoaffective depressive patients who become bipolar at follow-up. It is a much more unstable diagnostic entity, but it should be retained to reflect uncertainty. Previous episodes of "pure" mania or depression and family history again help to discriminate.

7.5. 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. In a first episode, it may be impossible to distinguish or to make a definitive diagnosis. Patient history and family history should be useful in confirming a diagnosis. It is most difficult in a catatonic stupor. It is important not to be sidetracked by the confusion of mania and delay treatment for a long time (1 week) while completing extensive organic workups.

7.6. 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, the premorbid adjustment should be stable, and this should be a change in behavior that could not have been expected or anticipated. Depressive symptoms or, less commonly, 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.

7.7. Suicide Attempter

Because a suicide attempt may be trivial or serious in a bipolar depressive or manic patient (rarely), all suicide attempters should be considered potential bipolar patients. Onset, symptoms, previous history, premorbid adjustment, and family history should help in making a diagnosis. This is especially true of suicidal, psychotic teenage depressive patients.

7.8. Attention Deficit Hyperactivity Disorder in Children and Adolescents

The debate regarding the comorbidity of bipolar disorder and attention deficit disorder continues (228). At this time, without a biologic marker, it is best to conclude that children and adolescents evaluated for bipolar disorder must have episodic illnesses. In addition, other children who are more chronically moody suffer from high rates of comorbid disruptive behavioral disorders that include attention deficit hyperactivity disorder (ADHD) (229, 230). A colleague of mine with expertise in childhood ADHD claims he has never seen mania in his well-studied patients or school-identified populations.

8. Treatment

8.1. Acute Mania and Mixed Episodes

No psychosocial management can be accomplished with a patient in the manic state. The patient is talkative, irritable, 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. In my opinion, 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. In the collaborative study of mood disorders in St. Louis, the first death in the follow-up period was in a manic patient who was killed in a fight in a bar. If manic patients have other illnesses, such as hypertension, that are controlled by medication, those illnesses get out of control as the manic 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, because 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 develop in such patients if telephone use is not restricted. Hospitalization is also welcomed by 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. Such patients are also super alert; they hear and interpret every sound and see and interpret everything in their visual field. 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. (231, 232) outlined a series of interpersonal behaviors that they had originally thought were part of the manic patient's premorbid personality but 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 led 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. This is best done by setting limits in an unambivalent, firm, and rather arbitrary way.

In acute mania, the efficacy of lithium 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 alone or in combination, 3) anticonvulsants such as valproate or carbamazepine alone or in combination with lithium, or 4) 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 thought that haloperidol alone was sufficient for the acute illness. Because there have been a few isolated reports that the combination of haloperidol and lithium can produce adverse side effects (233, 234), and because bipolar patients are at increased risk for tardive dyskinesia (235–237), more recent investigators have used lorazepam (1–2 mg every 4–6 h) or clonazepam (1 mg every 4–6 h) for sedation. The newer second-generation antipsychotics, such as olanzapine, risperidone, quetiapine, ziprasidone, and aripiprazole, have all been approved for the treatment of acute mania.

Before beginning treatment with lithium, the patient should have a complete medical workup, including 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. Lithium is not contraindicated, however, in patients taking these drugs or with hypertension alone. Lithium should not be started in a pregnant woman. The issue of becoming pregnant while on lithium maintenance is discussed in Sect. 8.5. Patients should be monitored daily for symptoms of toxicity, such as tremor, nausea, vomiting, diarrhea, and confusion. Lithium levels should be monitored frequently. Symptoms of toxicity necessitate immediate change in the lithium dose. In general, however, if the dose is raised gradually, toxicity can be avoided. Skin rash is another potential problem.

The usual starting dose of lithium in acute manic attack is 300 mg three times a day, which is gradually raised until a blood level of 1.0 to 1.2 mEq/L is achieved. Many patients need more than 1,500 mg of lithium a day to achieve this. Once the patient has shown the ability to tolerate the lithium, the dose should be switched to a single evening dose. That may be better for the kidneys. Improvement typically occurs in 8 to 10 days. Unfortunately, sometimes the patient may be discharged from the hospital long before the illness has run its course, only to be readmitted shortly after discharge. The manic patient should have a marked decrease in symptoms and an awareness regarding the illness and be

thoroughly committed to continuing lithium, before they are discharged (238). In addition, the patient's family should be educated and have understanding regarding the illness.

8.2. Other Treatment Therapies

All of the second-generation antipsychotics are also indicated for the treatment of mania. There are no definitive measures that must be taken before any of these medications are started, but it probably is important to weigh the patient and measure their waistline. The doses recommended are as follows: 2 to 6 mg/day risperidone; 10 to 20 mg/day olanzapine; 400 to 800 mg quetiapine in divided doses; 80 to 160 mg/day ziprasidone, again in divided doses; and 30 mg/day aripiprazole. The side effect profiles of each drug are slightly different, as are the presumed modes of action. The major drawback to some of them is weight gain, metabolic syndrome, and onset of diabetes, but, as we have already noted, there seems to be some relationship between bipolar illness and diabetes, independent of medications.

Valproic acid also has been shown to be effective by double-blinded, placebo-controlled studies in the treatment of acute mania (239–242). 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 usual starting dose is 750 mg/day in a divided dose, raised after 2 days to 1,000 mg and after an additional 2 days to 1,250 mg. The goal is to achieve a blood level of somewhere between 90 and 120 ng/ml (243). Doses need to be adjusted if used with other mood stabilizers such as lamotrigine.

Carbamazepine XR is useful in the treatment of the acute mania (244–248). Although the numbers are small in all studies, it seems to be a worthwhile choice for select patients. The average daily dose varies across studies from 200 to 800 mg twice daily, and the average blood level to be achieved varies between 6 and 12 ng/ml. Before beginning, a complete blood count and liver function tests are recommended. It too can produce an elevation of liver function tests and can reduce white blood cell and platelet counts that are dose related but do not predict the rarely seen aplastic anemia or agranulocytosis. These last two drugs are pharmacologically different. Carbamazepine induces its own metabolism, causing the blood concentrations to drop so that an upward adjustment of medication is often necessary. Because it induces liver enzymes, it also may make blood levels of average doses of valproate lower if it is started. In contrast, blood levels need to be monitored closely if carbamazepine is discontinued. Other drugs also may have their concentrations reduced during treatment with carbamazepine, notably all of the neuroleptics and birth control pills.

It is necessary to monitor the blood levels of these antimanic drugs as they are being first administered. After reaching a stable dose, steady-state values can be expected for lithium in 4 days, for carbamazepine in 3 days, and for valproic acid in 2 days. All drugs can be used together with antipsychotics, thyroid medication, and most antidepressants (not the MAO inhibitors). Drug monitoring is not necessary for the atypical antipsychotics.

Although it is said that the anticonvulsants are particularly useful for mixed or dysphoric mania and for rapid-cycling patients, one study that compared lithium with valproate did not sustain this claim (249). Swann et al. (250) reported that divalproex did treat the dysphoric subtypes better than lithium (see also reference [251]). These drugs should be used as second choices when a patient is nonresponsive to lithium or when the side effects of lithium are disturbing, particularly polyuria, weight gain, or acne. It is also said that if the patient has psoriasis, one of these drugs is preferable. Side effects are further discussed in Sect. 8.5.

McCabe (252) compared manic patients treated with ECT with untreated matched control subjects who were gathered before the introduction of ECT. In a second paper (253), a third group of patients treated with chlorpromazine was added. McCabe 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, but there were no significant differences between the two treatments. He did not, however, have a comparison group of patients treated with lithium. Black et al. (254) retrospectively compared ECT and lithium and found that patients treated with ECT (unilateral or bilateral) had a significantly greater percentage who showed marked improvement, especially with schizoaffective disorder, manic type. Small et al. (255) compared lithium treatment and bilateral ECT in patients randomized to treatment and found ECT better in the first 8 weeks but no difference in longer outcomes. Finally, Mukherjee and Debsikdar (256) reported a very favorable outcome in India in 30 manic patients treated with unmodified ECT. It seemed particularly good for dysphoric mania and severe cases. It also should be considered in those patients who have had such frequent episodes that lithium is not efficacious. Many authors have shown that the rapid-cycling patient is a poor responder to most pharmacotherapy; there have been no studies treating such patients with ECT.

8.3. Treatment of the Depressive Episode

Lamotrigine is, without a doubt, the most exciting new treatment for bipolar illness seen in 25 years. Unfortunately, it is only indicated for maintenance treatment. When one considers that although the hallmark of bipolar illness is mania, at least two thirds of the morbidity of this disorder is depression, a treatment that works on the depressive pole of the illness is welcome. Because of the dangerous side effect of skin rash, lamotrigine administration is started low and slowly: 25 mg orally for 2 weeks, then 50 mg for 2 weeks, then 100 mg for 4 weeks, and finally 200 mg once daily. The dose regime changes if patients are taking Tegretol, valproate,

and some other medications. It should be administered in the morning because it is an energizer. Usually patients feel calmer by the time they have been on 50 mg lamotrigine for a week.

Quetiapine is also indicated for bipolar depression in doses of 300 to 600 mg/day in divided doses, as is the olanzapine plus fluoxetine combination.

As stated earlier, there is still much controversy regarding using antidepressants in bipolar patients. However, many clinicians might agree with Altshuler et al. (257) and McElroy et al. (258) that maintenance of antidepressant treatment in combination with a mood stabilize may be warranted in some patients with bipolar disorder. An excellent review (259) concluded that, although antidepressants can be used for short-term management of depression, their extended use is controversial. The review, however, does not assure the reader that the patients' doses of maintenance mood stabilizers were optimal (see below). The clearest example is that rapid-cycling patients should be maintained on antidepressants with caution.

8.4. Maintenance Therapy

Before beginning, it must be said that whatever drug is used for maintenance, it is essential that the dose be maximized. Even if the patient is at the lower end of the dose range for one of the mood stabilizers, if depressive or hypomanic symptoms emerge, the maintenance drug dose should be increased before adding an antidepressant or some other agent. Small increases in doses will not raise the blood levels above the maximum recommended level but they may protect the patient from symptoms of the disorder. It is the real "key" to treating bipolar patients well. The American Psychiatric Association's (APA) treatment guidelines on bipolar illness recommend maximizing the dose as the first step in the treatment of this illness (260).

Everyone agrees that lithium is an effective prophylactic agent and is the "gold standard" for maintenance therapy (261, 262). Not only does it significantly decrease the number of manic episodes, but it also decreases the number of depressive episodes and dramatically decreases the outcome of suicide. This may occur because lithium decreases the number of manic episodes, and, because the illness is frequently biphasic or triphasic, it automatically decreases the potential for depressive episodes. In addition, the quality of the episodes that do occur is changed (shorter, less severe), and hospitalization is 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. Gelenberg et al. (263) have shown that lithium plasma levels need to be maintained between 0.8 and 1.0 mEq/L. New data indicate that lithium can be given in a single bedtime dose that can be either lithium carbonate or a sustained-release lithium. Controversy reigns regarding whether this is better for the kidney; however, most agree that compliance is increased with a single daily dose. The association between relapse and plasma lithium levels is still unclear, partially because the half-life of lithium is short and plasma levels fall quickly with missed doses and rise rapidly with extra doses, giving spurious impressions of compliance.

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, unlike carbamazepine and valproic acid, is approved for maintenance therapy for bipolar patients because of its action in preventing depressive relapses. More recently, olanzapine and aripiprazole, administered alone, have been approved by the US Food and Drug Administration (FDA) for maintenance because both have been shown to prevent relapse into mania, depression, or mixed episodes. The doses are similar to those used for acute mania.

Reanalysis of the NIMH collaborative study of bipolar patients showed that if the patient presented with mania, lithium or lithium plus imipramine was efficacious, whereas if the patient presented with depression, the combination was the best treatment (264). This speaks against antidepressants causing rapid cycling, an area of unresolved controversy (265). Others also have shown that lithium alone is not the best maintenance for those who present with depression (266).

As mentioned earlier, all investigators have found that rapid-cycling patients (four episodes per year) have the poorest lithium response. They relapse quickly. Studies indicate that the more quickly the relapse occurs after beginning maintenance therapy, the more likely a second relapse will occur. The converse is also true; that is, the longer the patient is maintained without relapse, the better is their long-term prognosis. Early relapse is not correlated with anything else, such as sex, age, age of onset, or family history (267, 268).

The question of when to start maintenance therapy is still unanswered. Everyone would agree that a patient with two severe manic or depressive episodes within a certain period should be started on maintenance therapy. Some would automatically start every patient on maintenance therapy after the second manic or schizoaffective manic episode. Age, age of onset, severity of episodes, length of episodes, and many other factors must be considered in making a decision.

All data show that there is a tremendous risk of recurring episodes (even an increased risk) if lithium maintenance is discontinued, therefore it is not recommended (269, 270). As might be expected, those who had been without episodes for the longest period before discontinuation were the least likely to experience relapse. Even with a pregnancy, lithium should be discontinued gradually and the patient followed very closely.

A 45-year-old successful businessman came for consultation regarding a decision to stop lithium. He had had several manic episodes in his 20s and finally became well stabilized on lithium. He had discontinued it at age 37 years and done

well for 3 years. He then developed a severe prolonged depression, during which time, he shot himself in the chest in his psychiatrist's office. After his recovery from depression via ECT, he was stabilized on lithium and had done well. Again, he wanted to stop lithium because of weight gain and tremor. It was not encouraged. Now a different maintenance treatment would be recommended, but weight gain is a problem with all except maybe the addition of certain antidepressants.

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

Jamison and Goodwin (271) have outlined the therapeutic issue surrounding maintenance therapy with lithium, including patient and physician compliance. O'Connell et al. (272) also discussed family and psychosocial factors in the outcome of lithium-maintained bipolar patients, as did Clarkin et al. (273). This is an important point, because when the literature on maintenance therapy is reviewed, there are far more relapses in collaborative treatment studies of multiple impartial investigators than in studies reported by individual therapists treating a cohort of patients. It is definitely a disorder in which therapy and management make a difference

It should be noted that stereotactic tractotomy is still being used for the most resistant cases (274, 275).

8.5. Side Effects of Antimanic Drugs

The side effects of lithium are numerous and disturbing to the patient but seldom deleterious to his or her health. Many patients complain of tremor while taking lithium. This can be treated with 10 mg propranolol, although it need not be given on a regular basis but can be taken by the patient before those situations that might prove embarrassing. Weight gain is a problem. Almost 50% of patients gain some weight, and weight gains of up to 30 kg have been reported. Weight gain, for the most part, is caused by increased caloric intake and not water weight and needs to be treated with a low-carbohydrate diet. Patients should be warned not to treat an increased thirst with calorie-laden drinks. Some patients develop polyuria and polydipsia, and some patients cannot concentrate their urine. If this occurs, an adjustment in the dose of lithium should be made. Careful studies of long-range effects do not indicate permanent kidney damage (276). Memory problems, tiredness, and a dulling of senses have been reported to be present while the patient is taking lithium, although these also could be symptoms of a low-grade depression. Certain antidepressants or psychostimulants may be helpful. Some patients report diarrhea. A few patients develop hypothyroidism while taking lithium. If this occurs, thyroxine needs to be added to the drug regimen. A few patients develop leukocytosis. Finally, some patients develop alopecia.

Because there are reported prenatal deaths and congenital malformations in babies of women taking lithium, lithium should be discontinued, if possible (277), before pregnancy. Carbamazepine and valproate have associated teratogenic effects and they should not be used in women who are trying to become pregnant. Many of the side effects described above are also reported with the anticonvulsants, although supposedly the cognitive dysfunctions are less with valproate. All acute and maintenance dose side effects should be discussed with the patient and the family. To date, the second-generation antipsychotics are not associated with birth defects and may be the treatment of choice during pregnancy.

8.6. 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 with those not treated with lithium, taking lowered doses of lithium, and taking anticonvulsants (278). A recently published follow-up of 72 bipolar I patients followed prospectively for up to 10 years confirmed the finding (279). Not only were the patients who were highly adherent to long-term treatment with lithium less likely to attempt or complete suicide, but they also had less hospitalizations, less hypomanic–manic illness and less substance abuse than those who demonstrated low compliance.

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5
Major Depressive Disorder

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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 jhysettings, 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 chapter on this topic in the previous iteration of this book was titled "Unipolar Depression" and was written by one of my mentors, George Winokur. Much of our current understanding of mood disorders emanates from the research of Winokur and his colleagues. I am delighted to have the opportunity to write this chapter.

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 control subjects formed the basis of the disorder. Symptoms that 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, and the clinical classifications used by the Washington University group were summarized by Feighner et al. (3). Winokur (4) further proposed that unipolar depression might be divided into three groups: " depression spectrum disease"—individuals who were depressed and had a first-degree relative who had alcoholism or antisocial personality disorder; "familial pure depressive disease"—depressed individuals who had a family history of depression but not of alcoholism or antisocial personality disorder; and "sporadic depressive disease"—depressed individuals who had no family history of depression, alcoholism, or antisocial personality disorder. This classification system is no longer in clinical use but is of interest in that it was one of the first clinical classifications in psychiatry to use both clinical symptoms and family history.

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

1. Definition

The term unipolar has been dropped from the official nomenclature of *Diagnostic and Statistical Manual*, 4th edition, text revision (DSM-IV-TR) and replaced by major depressive disorder (MDD). MDD is characterized by one or more major depressive episodes—2 weeks or longer 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), depression caused by substances that may cause this syndrome (some anti-hypertensives or stimulants) or if the syndrome is brief—shorter than 2 months—and related to bereavement. Persons with depressive symptoms that persist

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longer than 2 months and otherwise meet criteria for major depressive episode are rediagnosed as MDD because some research suggested that the usual course of depressive symptoms in uncomplicated bereavement was brief. A brief depression 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-IV-TR is the current standard for classification. Worldwide, the International Classification of Diseases (ICD) system is used.

DSM-IV-TR lists several subtypes and course modifiers for MDD. "With melancholic features" includes subjects who have of 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 that 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.

Course modifiers include recurrent, chronic, with incomplete remission, and with antecedent dysthymia. "Recurrent" denotes multiple major depressive episodes that are separated by at least a 2-month period of either euthymia or depressive symptoms insufficient to meet the criteria for major depressive episode. "Chronic" is diagnosed if MDD persists for 2 years or longer. "With incomplete remission" is diagnosed if there are residual depressive symptoms after the subject no longer meets criteria for major depressive episode and these symptoms do not themselves meet criteria for major depressive episode. "With antecedent dysthymia" is diagnosed if the major depressive episode was preceded by dysthymic disorder—a depressive condition characterized by 2 years or greater of depressive symptoms present more days than not or depressive symptoms that do not meet criteria for a major depressive episode—such as having fewer than the five of nine symptoms of a major depressive episode present every day.

Depression severity can be characterized as mild, moderate, or severe. Determination of severity can be made clinically or by the use of rating scales that had been standardized to determine levels of severity of depressive symptoms during the past week (5–9).

2. Epidemiology

Two recent epidemiologic studies suggest that MDD is very common and also occurs with high rates of comorbidity (complicated by the presence of other psychiatric disorders) (10, 11). The national comorbidity survey reported a lifetime prevalence of MDD of 12.7% in male patients, 21.3% in female patients, and overall, 17.1%. The national comorbidity survey replication study showed similar data. Thus, MDD is a common condition and occurs in women more frequently than in men. In contrast, bipolar mood disorders are estimated to have a lifetime prevalence of 6 to 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.

3. Clinical Picture

Although the criteria for a major depressive episode is 2 weeks or longer, most episodes last much longer and the mean duration of an episode of MDD is generally 6 to 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 defined in DSM-IV-TR as 2 years or longer of depression, and approximately 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" (12). We have questioned whether the distinctions made among the chronic forms of depression (chronic MDD, dysthymic disorder, MDD with incomplete remission where the disorder lasts 2 years or longer, and double depression) are meaningful (13).

As mentioned, MDD is 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 approximately 15% of patients who experience significant depression will ultimately die by suicide. The rate of suicide in the United States is approximately 10 to 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 (14, 15).

Depression can complicate medical conditions and, if one has a medical condition, the depression is frequently worse. Again, it is important to exclude 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 early ages of onset, and the differential diagnosis of depression in younger individuals should include consideration of bipolar disorder.

4. Depressive Subtypes

There are several subtypes of depression. Approximately 20% of patients with MDD will have chronic depression and approximately 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 effect a response. Recurrent depression requires maintenance therapy 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 therapy (ECT) or a combination of an antidepressant and an 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 MDD. In fact, MDD represents 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. Etiology

The etiology of MDD is 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 (16). 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. 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 a negative life event.

6. Biological Theories of Depression

One recent compelling theory regarding the pathogenesis of depression involves the hypothalamus, pituitary gland, the adrenal gland, and cortisol production—the hypothalamic–pituitary–adrenal (HPA) axis (17,18). In this model, depressed patients have elevated levels of cortisol. These elevations in cortisol levels are thought to reflect an abnormality in the HPA axis regarding response to stress—an inability to shut down the production of hormones that regulate the production of cortisone because of an impaired "feedback" loop. The effect of elevated cortisol levels is to cause toxicity in the hippocampal regions of the brain resulting in hippocampal shrinkage, presumably through lowering levels of brain-derived neurotrophic factor (BDNF). 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 as adults (19, 20). Furthermore, patients with severe depression have elevated cortisol levels and also have smaller hippocampi than control subjects (21, 22).

Another theory regarding the pathogenesis of depression involves dysregulation of catecholamines (23, 24). Central nervous system norepinephrine deficiencies were thought to mark depression because drugs that increased norepinephrine levels in brain also were effective clinically in treating depression. The advent of the SSRIs led to a compelling theory that serotonin dysregulation was involved in the pathogenesis of depression. This theory was based on the notion that low levels of serotonin in brain might be the cause of depression because the effect of SSRIs was to increase serotonin neurotransmission in brain.

Recent studies link abnormalities of the serotonin transporter gene to depression (25). One study showed that individuals with the short allele form of the serotonin transporter gene (*ss*) were more likely to be susceptible to depression and response to adverse life stress than individuals with the long form of this gene (*sl* or *ll*). Another study recently reported that a group of patients who had the *ss* form of this gene were more likely to show an antidepressant response to augmentation with a particular compound than other patients (Michelson DA, unpublished data). These are all preliminary studies that need to be replicated, but they highlight the need for studies that show a correlation of genetic data with clinical outcome.

7. Laboratory Studies

No definitive laboratory tests reliably demonstrate that one group of depressed patients differs from another group of depressed patients or that depressed individuals can be reliably differentiated from healthy subjects or from nondepressed individuals (26). 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 in control subjects. However, this test failed to reliably demonstrate differences between patients and control subjects and it is no longer widely used, even in research settings. Other tests reported to have abnormal results are a blunted thyroid-stimulating hormone (TSH) response to thyrotropin-releasing hormone (TRH). This test is also not currently in vogue.

Depressed patients frequently have sleep abnormalities and a striking sleep abnormality among depressed patients is shortened rapid eye movement (REM) latency. This finding has been replicated but is of little diagnostic use.

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.

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 during 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 (27). It is very 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 (BDI) (7), the Patient Health Questionnaire (PHQ)-9 (8), or the Quick Inventory of Depressive Symptoms (QIDS) (9)—patient self-rating scales—were applied uniformly to patients presenting in primary care settings, just as 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 present 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 (28). 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 whether previous episodes have occurred, a family history to determine whether 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 exclude before a diagnosis on 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 excluded with simple laboratory testing—complete blood count to exclude anemia and thyroid screen to exclude hypothyroidism or hyperthyroidism. Other laboratory tests may be indicated if there are particular symptoms or signs that suggest the need for such testing. Because some medications may cause depression, a review of medication changes in the patient in relation to depressive onset is important. Bipolar disorders can be excluded by asking about hypomanic or manic symptoms occurring just before or after depressive episodes. Approximately 5% of patients who are experiencing their first depressive episode are bipolar, and this diagnosis usually cannot be made until the patient exhibits hypomania (29). 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 (30). 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 because patients frequently deny these conditions. A substance use and alcohol history are important to ascertain, and urine toxicology testing may be helpful if substance use is suspected.

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 that 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 MDD 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.

10. Principles of Treatment

The principles of treatment of MDD have been well established during the past 2 decades. The goal of treatment is to achieve remission and also recovery. Remission is defined as a sufficient absence of depressive symptoms to generate a rating of seven points or less on the 17-item Hamilton Depression Rating Scale (5). The Hamilton Depression Rating Scale is a clinician-rated, standardized scale for assessing depression severity. Recovery currently is defined by at least 2 months of a remitted state. The rating scales noted in Sect. 8, BDI (7), QIDS (9), and PHQ-9 (8), 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 nine points or less, on the PHQ-9 is four points or less, and on the QIDS is five points or less. Depression needs to be considered a lifelong disorder because it is often chronic and frequently recurrent. In situations in which 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. To do this, patients need to be treated through an acute treatment phase, usually of approximately 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 to 9 months longer. Thus, the initial episode of depression should be treated to remission and should have the treatment continued for approximately a year (31, 32). 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 to keep a mood calendar to determine whether 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 (33, 34).

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 to 12 weeks of treatment is usually recommended. A recent research study, the STAR*D study, may provide guidelines regarding treatment of depression. The STAR*D study involved several thousand patients with major depression who were treated mostly in primary care settings (35, 36). 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. Approximately 28 to 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 to achieve an optimal outcome for depressed patients.

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 optical outcome, data to support this notion are generally not found in research studies.

11.1. Psychotherapy

We recommend psychotherapy alone for patients who have a first episode of depression that is mild. Psychotherapies that have been studied for major depression and shown to be effective include cognitive–behavioral psychotherapy (CBT),

interpersonal psychotherapy (IPT), behavioral activation (BA), cognitive behavioral analysis system of psychotherapy (CBASP), and some others. 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. For patients with moderate depression (Hamilton depression rating scores of 18–24 points on the 17-item scale) we recommend beginning with pharmacotherapy and, if patients do not achieve remission at an adequate dose of pharmacotherapy, to consider adding one of the psychotherapies noted above. It is our belief that psychotherapy is less effective as the severity of depression worsens. CBT, IPT, BA, and CBASP have all been shown to be effective in reducing relapse and recurrence in depressed patients (37–40).

11.2. Pharmacotherapy

We recommend pharmacotherapy alone 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 ECT may be the best treatment. If the patient has psychotic depression, the combination of an antidepressant and antipsychotic medication is helpful, although ECT 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 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), the newer antidepressants (venlafaxine, duloxetine—serotonin/norepinephrine reuptake inhibitors [SNRIs], and bupropion, mirtazapine, trazodone, and nefazodone). Older antidepressants include the tricyclic antidepressants (amitriptyline, imipramine, doxepin, nortriptyline, protriptyline, trimipramine, and desipramine) as well as the MAO inhibitors (tranylcypromine, phenelzine, and selegiline).

Within the SSRI class, the most common side effects are gastrointestinal (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 depressive patients is recommended. Approximately 15% of patients treated with SSRIs develop insomnia and approximately 15% experience sedation. Weight gain is usually not a problem with the SSRIs, with the exception of paroxetine; a small percentage of patients will gain a significant amount of weight with paroxetine. 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 US Food and Drug Administration (FDA)-approved

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	50–150 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		
Tranylcypromine	20–60 mg	
Phenelzine	45–90 mg	
Selegiline transdermal system	6–12 mg/24 h	Administered as a patch
The above are MAO inhibitors and have several food and medication prohibitions to prevent severe hypertensive episodes		

*Editor: This range may provide the best response and is verifiable by checking serum level of 50–150 ng/ml (SI: 190–570 nmd/l).

TABLE 5.2. Newer antidepressants and their doses.

Drug	Doses	Comment
Fluoxetine	20–60 mg	
Sertraline	50–200 mg	
Paroxetine	20–60 mg	
Citalopram	20–60 mg	
Escitalopram	10–20 mg	
The above are SSRIs and share common side effects of nausea, insomnia, sedation, and sexual dysfunction. As a class, these medications are also approved for the treatment of bulimia, panic disorder, generalized anxiety disorder, posttraumatic stress disorder, social anxiety disorder, and obsessive–compulsive disorder. They are safer in overdose than tricyclic antidepressants and do not have the severe food and medication interactions that typify the MAO inhibitors. Blood level monitoring is generally not useful		
Venlafaxine	75–375 mg	Hypertension can occur at doses >300 mg
Duloxetine	60–120 mg	
Mirtazapine	15–60 mg	
Nefazodone	300–600 mg	
Bupropion	150–450 mg	Seizures can occur at doses >450 mg
Trazodone	100–600 mg	Priapism can occur in male patients
Venlafaxine and duloxetine are SNRIs. Their common side effect is nausea. Mirtazapine is highly sedating. Bupropion is the least sedating of the antidepressants. Nefazodone has been rarely associated with liver toxicity. Bupropion and nefazodone are both weight neutral with long-term use and also do not cause sexual dysfunction.		

for treatment of panic disorder, social phobia, generalized anxiety disorder, posttraumatic 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 do not have similar side effects. Venlafaxine and duloxetine are SNRIs. Their common side effects include nausea on initiation of treatment. Sexual dysfunction seems 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. FDA has recently approved duloxetine for generalized anxiety disorder.

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 because 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 whether 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 has 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 effects the 3A4 liver isoenzyme system. The major side effects of nefazodone are sedation and there is a need for complicated dose titration to achieve a therapeutic dose range. Nefazodone does not seem to cause weight gain, sexual dysfunction, or a discontinuation syndrome. Rare cases of liver toxicity have been reported with nefazodone, and the use of this drug is infrequent in clinical practice. Nefazodone is approved by the FDA for treatment of major depression.

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 affects 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. Before the advent of the SSRIs in the United States, the tricyclic antidepressants were first-line treatments. However, their multiple side effects and 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 MAO in the 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 MAO and, therefore, low doses of the patch permit the dietary intake of tyramine-containing foods. Selegiline is also 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.

11.3. Physical Treatments for Depression

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

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 (41). 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 administered succinylcholine to temporarily paralyze muscles so there is no pronounced physical movement during the convulsion. The treatments are usually administered three days a week and an average of 8 to 10 treatments is typical to improve a severe depressive state. Some patients relapse quickly after ECT is stopped and they may require ECT administration on a long-term basis for maintenance treatment. Antidepressant medication should be administered after an ECT series to reduce the likelihood of relapse (42). Side effects of ECT include confusion, which usually clears after each treatment, and permanent memory loss for some of the days when the treatments were administered.

VNS was recently 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 that is transmitted into the brain and affects a number of brain areas that are thought to be important in relation to mood disorders. Because VNS involves a surgical procedure, there is a small—approximately 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 s every 5 min), 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 (43). 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 approximately 10% of such patients improved after 1 year of usual treatment in the community and the improvement in these patients was usually not sustained (44). In contrast, with VNS therapy,

approximately a third of the patients markedly improved, approximately a third of the patients improved somewhat, and approximately a third of the patients did not change after 1 year, and the improvement noted in patients tended to be sustained once it occurred (43).

As of the time this chapter was written, TMS was experimental. However, FDA approval for this treatment is expected in 2008. TMS involves the placement of a magnet on the outside of the head near the left temporal area of the brain. This magnet generates a current that penetrates the skull and affects brain waves and brain function. TMS has been used experimentally for patients with treatment-resistant depression, and the results of these research studies show that approximately a third of the patients will respond in a 3-week period compared with approximately 10% of patients who are treated with a "sham" treatment (45,46). TMS is administered 5 days a week for approximately 45 minutes per session. Some data suggest that individuals whose current episode of depression has been longer than 5 years will not respond to TMS.

The other treatments listed above, MST and DBS, are experimental at this time. Whether these treatments will be developed for clinical use is unclear.

11.4. Treatment-Resistant Depression

Approximately 70% of patients who undergo treatment for a depressive episode respond, and approximately 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 on 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 in Sect. 11.3, 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 caused by 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, or 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 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 (47).

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

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, very 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. Johns Wort was in wide popular use several years ago, but a controlled study later demonstrated that it was not effective in moderately depressed patients (48). 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 studied to demonstrate their efficacy, and many have passed the test. Whether other psychotherapeutic modalities are effective remains for future evaluation.

12. Summary

Major depression is a common condition that 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

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Abstract In this chapter, I 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 Etiology · Schizophrenia · Treatment

1. History

Schizophrenia is a debilitating disease of the brain that 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 that 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 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 a 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, although these symptoms are helpful in diagnosis of schizophrenia, they are not specific to this disorder.

2. Current Diagnostic Criteria

The current criteria used presently to diagnose schizophrenia, is the product of years of empirical testing. The *Diagnostic and Statistical Manual*, 4th edition, text revision (DSM-IV-TR) criteria include:

A. *Characteristic symptoms:* Two (or more) of the following, each present for a significant portion of time during a 1-month period (or shorter if successfully treated):

   1) delusions
   2) hallucinations
   3) disorganized speech (e.g., frequent derailment or incoherence)
   4) grossly disorganized or catatonic behavior
   5) negative symptoms, i.e., affective flattening, alogia, or avolition

   Note: Only one Criterion A symptom is required if delusions are bizarre or hallucinations consist of a voice keeping up a running commentary on the person's

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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	

Schneider K. Clinical Psychopathology. New York: Grune and Stratton, 1959 (144).

behavior or thoughts, or two or more voices conversing with each other.

B. *Social/occupational dysfunction:* For a significant portion of the time since the onset of the disturbance, one or more major areas of functioning, such as work, interpersonal relations, or self-care are markedly below the level achieved before the onset (or when the onset is in childhood or adolescence, failure to achieve expected level of interpersonal, academic, or occupational achievement).
C. *Duration:* Continuous signs of the disturbance persist for at least 6 months. This 6-month period must include at least 1 month of symptoms (or shorter if successfully treated) that meet Criterion A (i.e., active-phase symptoms) and may include periods of prodromal or residual symptoms. During these prodromal or residual periods, the signs of the disturbance may be manifested by only negative symptoms or two or more symptoms listed in Criterion A present in an attenuated form (e.g., odd beliefs, unusual perceptual experiences).
D. *Schizoaffective and mood disorder exclusion:* Schizoaffective disorder and mood disorder with psychotic features have been excluded because either 1) no major depressive, manic, or mixed episodes have occurred concurrently with the active-phase symptoms; or 2) if mood episodes have occurred during active-phase symptoms, their total duration has been brief relative to the duration of the active and residual periods.
E. *Substance/general medical condition exclusion:* The disturbance is not caused by the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition.
F. *Relationship to a pervasive developmental disorder:* If there is a history of autistic disorder or another pervasive developmental disorder, the additional diagnosis of schizophrenia is made only if prominent delusions or hallucinations are also present for at least a month (or shorter if successfully treated).

3. Epidemiology

Schizophrenia affects 1% of the adult population in the world (9). The point prevalence of schizophrenia is approximately 5 per 1000 population (10) and the incidence is approximately 0.2 per 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 male patients, with mean ages of onset of 20 and 25 years in male and female patients, 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).

4. Genetics

Emerging evidence points to schizophrenia as a familial disorder with a complex mode of inheritance and variable expression (7, 12–14). Although single-gene disorders such as Huntington's disease have homogenous etiologies, complex trait disorders such as 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 monozygotic twins and 14% for dizygotic twins (7, 15). Consistent with this, a recent meta-analytic 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 versus 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 disrupted in schizophrenia (*DISC*)-1 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).

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
Reelin	*RELN*	7q22
Serotonin 2A receptor	*5HTR2A*	13q14-q21

From Sullivan et al., 2006 (12); Fatemi et al., 2005 (42); Wedenoja et al., 2007 (179).

Linkage and association studies (12, 20, 21) show 12 chromosomal regions containing 2,181 known genes (20) and 9 specific genes (12) being involved in the etiology of schizophrenia (12). Variations or polymorphisms in nine genes, including neuregulin 1 (*NRG1*), dystrobrevin-binding protein 1 (*DTNBP1*), G72 and G30, regulator of G protein signaling 4 (*RGS4*), catechol-O-methyltransferase (*COMT*), proline dehydrogenase (*PRODH*), *DISC1* and *DISC2*, serotonin 2A receptor (*HTR2A*), and dopamine 3 receptor (*DRD3*) have been associated with schizophrenia (Table 6.2).

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*	+	
Complexin 2	*CPLX2*	+	+
Distal-less homeobox 1	*DLX1*	+	
Dopamine receptor D1	*DRD1*	+	
Dopamine receptor D2	*DRD2*	+	+
$GABA_A$ receptor, subunit A1	*GABRα1*	+	
$GABA_A$ receptor, subunit A5	*GABRα5*	+	+
$GABA_B$ receptor 1	*GABBR1*	+	
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*	+	+
Proteolipid protein	*PLP1*	+	
Reelin	*RELN*	+	+
Regulator of G protein signaling 4	*RGS4*	+	
Short stature homeobox 2	*SHOX2*	+	
Synapsin 2	*SYN2*	+	

From Le-Niculescu et al., 2007 (14).

Another means of studying the genetic basis of schizophrenia uses the technique of DNA microarray (14,22). 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 control subjects; peripheral lymphocytes obtained from schizophrenic and matched healthy controls and antipsychotic-treated brains of rodents (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.

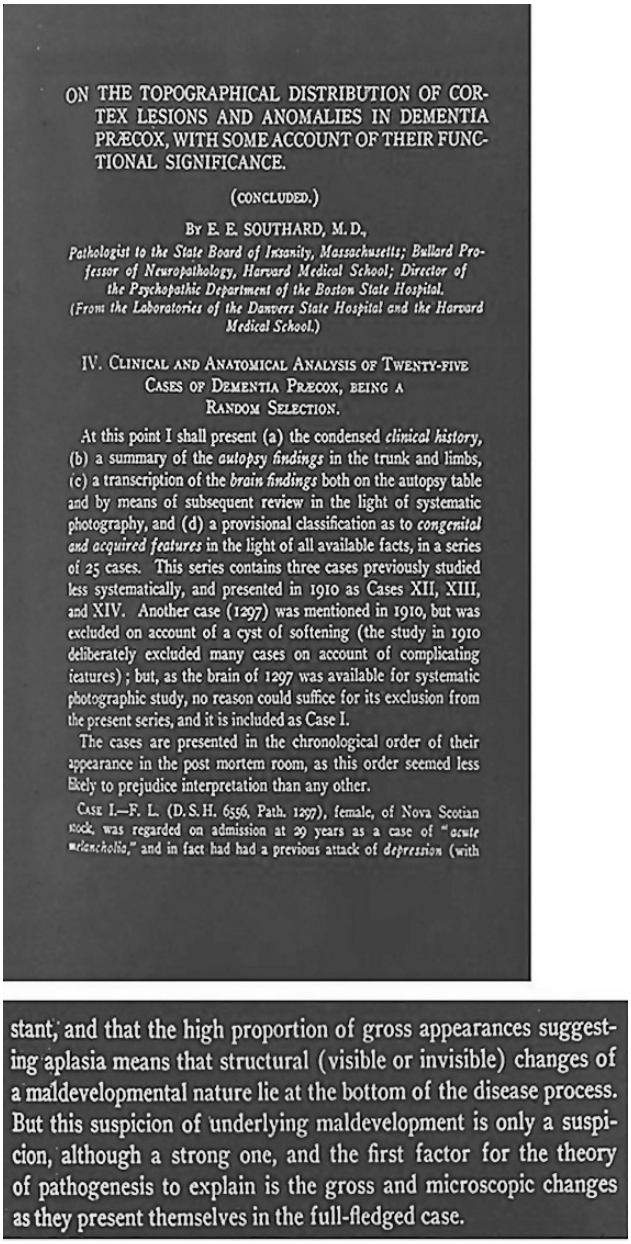
5. Etiology

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 (23) in children who later developed schizophrenia. Later, Southard (Fig. 6.1) reported on the presence of neuropathological signs in brains of subjects with schizophrenia that further pointed to maldevelopmental origins of this disorder (24).

5.1. Neurochemistry of Schizophrenia

5.1.1. The Dopamine Hypothesis

Dopaminergic tracts are composed of four branches: 1) the 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, 25); 2) the mesolimbic tract, originating from the ventral tegmental area and ending in hippocampus, amygdala, and ventral striatum, deals with cognitive/attentional, motivational, and reward systems (7, 25); 3) the 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 (26–28). The dopamine (DA) receptors are classified into two distinct families of D1-like (D1 and D5) and D2-like (D2, D3, D4) receptors (25). The D1 receptors are localized to prefrontal cortex (PFC) and striatum. The D2 receptors are localized mostly to striatum, but with lower concentrations in the hippocampus, amygdala, and entorhinal cortex. The D3 receptors are localized to the ventral striatum. The D4 receptors are present in the hippocampus and PFC. Finally, the D5 receptors are found in the hippocampus and entorhinal cortex (7,25). Presynaptic dopamine receptors such as D2 and D3 are localized to cell bodies or axon terminals of neurons (7). Dopamine helps in modulating glutamatergic inputs and pyramidal cell excitability (25).



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.,

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(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.

The dopamine hypothesis of schizophrenia is based on the assumption that dopamine hyperactivity causes psychotic symptoms, and that dopamine antagonists such as 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 such as LSD or psilocybin (acting on the serotonin system) or dissociative anesthetics such as ketamine or phencyclidine (PCP) (acting on the glutamate system) also cause psychotic symptoms (7, 25). A further limitation of this hypothesis is that consistent abnormalities have not been found in dopamine receptors or dopamine metabolites in subjects with schizophrenia (7,25,29). The two consistent postmortem findings include an increase in D2-like receptors in striatum of schizophrenic patients and lack of changes in striatal densities of D1 receptors or dopamine transporters (25). However, a recent finding of upregulated D1 receptor binding in the dorsolateral PFC (DLPFC) of schizophrenic subjects has been associated with impaired working memory performance (25).

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, 30–32). The number of various serotonin receptor types in the brain exceed 15, with the most important receptors being 5HT1, 5HT2, 5HT3, 5HT6, and 5HT7 (7). Inhibitory somatodendritic serotonin autoreceptors (5HT1A) are localized to raphe serotonergic neurons, which, on activation, lead to decreased firing of the neurons (7, 33). In contrast, terminal autoreceptors modulate synthesis and release of serotonin (7). 5HT3 receptors help to stimulate dopamine release (7). Additionally, pyramidal cells in the mesocortical areas bear postsynaptic 5HT2A receptors that subserve serotonin–dopamine interaction in various brain areas.

Although 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).

5.1.3. The Glutamate Hypothesis

Glutamate is the main excitatory neurotransmitter in the central nervous system (CNS) (7, 25). Approximately 60% of neurons and 40% of synapses of the brain are glutamatergic in nature (25). 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 that indirectly regulate electrical signaling by activation of various second messengers) consists of groups I, II, and III receptors (25). The glutamatergic hypothesis of schizophrenia is based on deceased levels of glutamate in the cerebrospinal fluid (CSF) of schizophrenic subjects (7, 26) and decreased expression of NMDA and AMPA receptors in the hippocampus and thalamus of schizophrenic subjects (25, 34–37). Additionally, use of noncompetitive and competitive antagonists of NMDA receptors can lead to production of positive, negative,

and cognitive symptoms of schizophrenia (29). Administration of clozapine can block the NMDA antagonistic effects of PCP (29). Several compounds, such as glycine, D-serine, and D-cycloserine, have been reported to reduce positive and negative symptoms in subjects with schizophrenia (25,29). Genetic evidence also points to involvement of several genes (*DAAO*, *G72*, *neuregulin*, *dysbindin*, *RGS4*) that impact the glutamate system in schizophrenia (25). Mice with alterations in NMDA receptors show hyperactivity and schizophrenic-like behaviors (38–41).

5.1.4. The GABAergic Hypothesis

Gamma-aminobutyric acid (GABA) is the major inhibitory neurotransmitter in the mammalian brain. Recent 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 (42,43) of schizophrenic subjects. Supportive data (44, 45) also point to decreases in GAD67 species in brains of subjects with schizophrenia. Furthermore, Reelin, an important factor involved in synaptic plasticity that colocalizes to GABAergic interneurons is reduced in brains of subjects with schizophrenia (42, 46–48) (Fig. 6.2 and Color Plate 1, following p. 650).

5.2. Neurodevelopmental Theories of Schizophrenia

The accumulation of a large body of evidence during the last century points to involvement of pathologic processes that begin in utero and lead to development of schizophrenia in adolescence (5, 49, 50). These neurodevelopmental abnormalities, beginning in utero, as early as late first or early second trimester (49, 51), 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 (51) 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 (52, 53). Elmer E. Southard, an American neuropathologist (54) who worked under Carl Weigert, visited Kraepelin's clinic and Franz Nissl's laboratory and produced the first convincing neuropathological study of schizophrenia (24, 54) that pointed to the maldevelopmental nature of schizophrenia (Fig. 6.1). Southard also inferred that the cause for these maldevelopmental lesions may have been insults that interfered with brain cell growth and development (24). Resurgence of biological psychiatric research in the last three 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 are discussed in the following sections.

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 (23). The complications observed

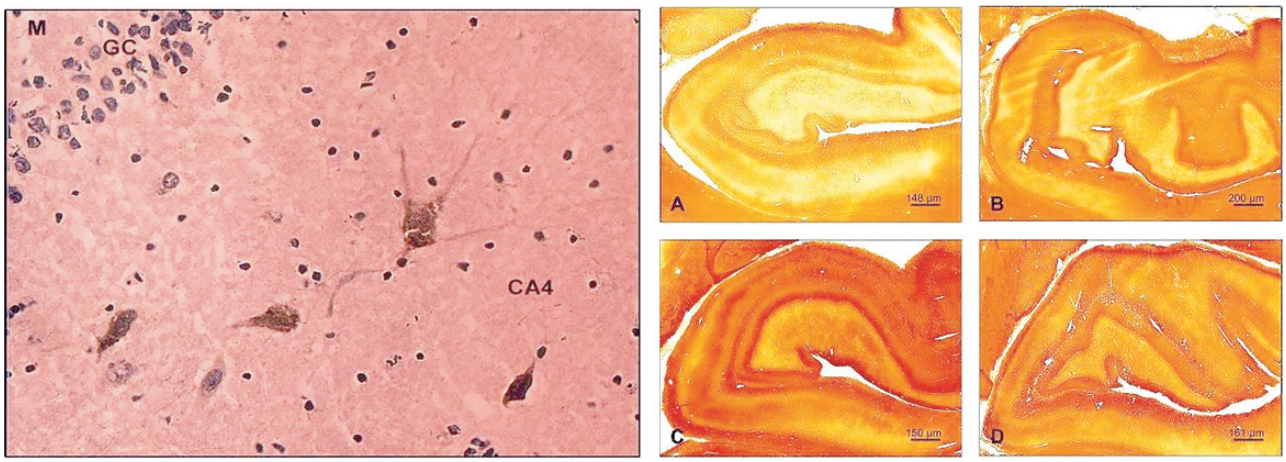

FIGURE 6.2. **a** Several Reelin-positive cells are localized to the hilus (CA4) of hippocampal complex. *M*, dentate inner molecular layer, *GC*, granular cell layer. Original magnification, ×40. **b** SNAP-25 immunostaining is localized to various layers of ventral hippocampus in subjects with bipolar disorder (**A**), major depression (**B**), and schizophrenia (**D**) compared with a normal control subject (**C**). Note the diminution in SNAP-25-specific immunostaining in the strata oriens and moleculare of patients with bipolar disorder (**A**) and schizophrenia (**D**) versus an increase in SNAP-25 depressed (**B**) and normal levels in control (**C**) subjects. The following hippocampal fields were identified and analyzed by densitometry: from the outside in, alveolus, stratum oriens, strata pyramidale, radiatum and lucidum combined, stratum moleculare (combined hippocampal layer as well as outer and inner dentate molecular layers), stratum granulosum, cornu ammonis (CA4) or hilus, cornu ammonis 3 (CA3), cornu ammonis 2 (CA2), subiculum, and presubiculum. (**a** Reprinted with permission from the Nature Publishing Group (47). **b** Reprinted with permission from Lippincott Williams and Wilkins (178)) (*see* Color Plate 1, following p. 650).

include periventricular hemorrhages, hypoxia, and ischemic injuries (7, 55).

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, cerebroventricular enlargement distinguishes affected from unaffected discordant monozygotic twins (Fig. 6.3). Furthermore, gross brain abnormalities have been identified in the DLPFC, hippocampus, cingulate cortex, and superior temporal gyrus (7, 29). 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 (56). More recently, 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 (Fig. 6.3 and Color Plate 2, following p. 650) (57).

5.2.3. Postmortem Histologic Studies

Numerous reports have documented the presence of various neuropathologic findings in postmortem brains of patients with schizophrenia (24, 58–61). These findings consist of cortical atrophy; ventricular enlargement; reduced volumes of hippocampus, amygdala and parahippocampal gyrus; disturbed cytoarchitecture in the hippocampus; cell loss and volume reduction in the thalamus; abnormal translocation of NADPH–diaphorase-positive cells in frontal and hippocampal areas (Fig. 6.4 and Color Plate 3, following p. 650); and reduced cell size in Purkinje cells of the cerebellum (58–60). However, by far the greatest abnormalities have been found in the prefrontal, ventral hippocampal, and cerebellar cortices of schizophrenic brains (61). Collectively, these data reflect abnormal corticogenesis during the mid-gestation period in schizophrenic patients. Additionally, several recent reports using magnetic resonance imaging (MRI) and diffusion tensor imaging (DTI) techniques have shown reduced white matter diffusion anisotropy (diffusion changes in water in white matter) in subjects with schizophrenia (62–64). 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 (62). Furthermore, reductions in white matter anisotropy reflect disrupted white matter connections, which supports the disconnection model of schizophrenia (65). 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 (62, 66–70). There are also negative findings showing no white matter abnormalities in schizophrenia (71, 72). 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 that develop later in life in subjects who become schizophrenic (73, 74). Several recent reports now indicate that either glial cells are dysfunctional (75–78) or unaffected in schizophrenia (79). 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).

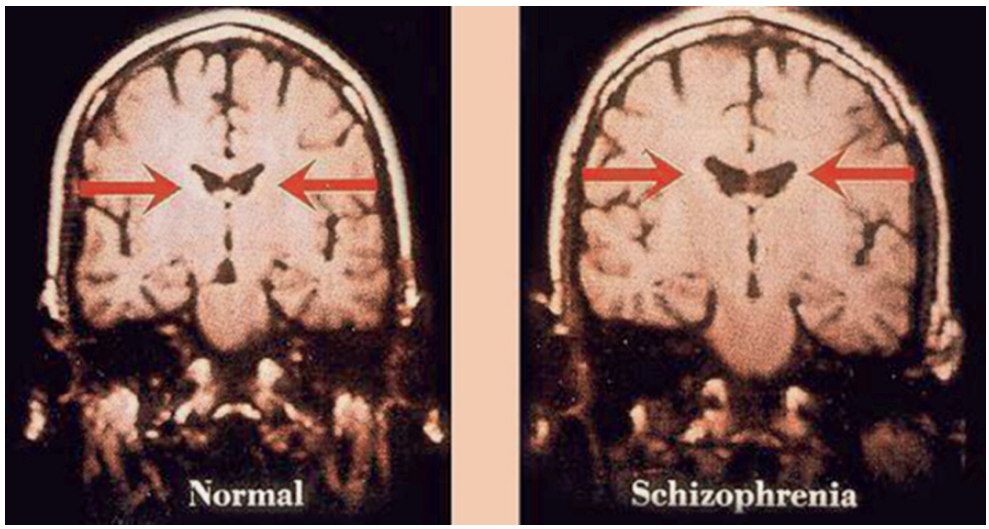

FIGURE 6.3. Ventricular size in monozygotic twins discordant for schizophrenia. Coronal MRI scans of twins discordant for schizophrenia show lateral ventricular enlargement in the affected twin (reprinted with permission from the Massachusetts Medical Society (179). All rights reserved) (*see* Color Plate 2, following p. 650).

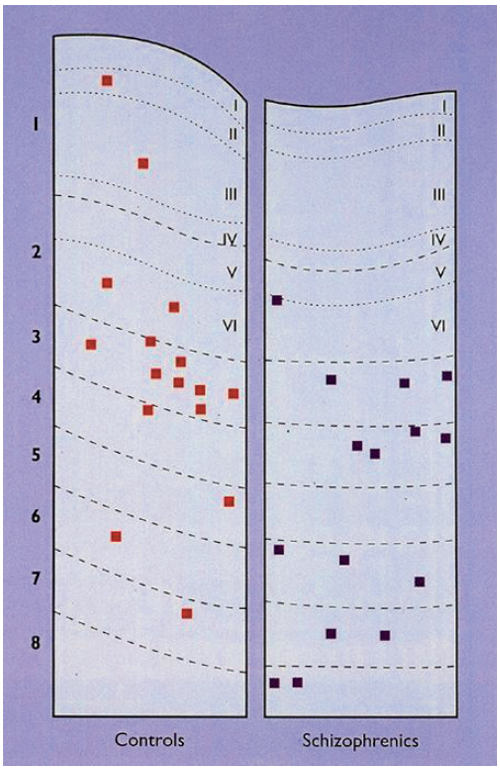

FIGURE 6.4. These camera lucida drawings compare the distribution of nicotinamide–adenine dinucleotide phosphate–diaphorase-stained neurons (*squares*) in sections through the superior frontal gyrus of a control and schizophrenic brain. There is a significant shift in the direction of the diaphorase positive neurons in the white matter in the schizophrenic brain. Numbers 1 to 8 indicate compartments of the brain; Roman numerals indicate the cortical layers (reprinted with permission from the American Medical Association (60). All rights reserved) (*see* Color Plate 3, following p. 650).

5.2.4. Biochemical Brain Marker Anomalies and DNA 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).

Several recent reports implicate various gene families as being involved in pathology of schizophrenia using DNA microarray technology, i.e., genes involved in signal transduction (74, 80–88), cell growth and migration (81), myelination (73,74), regulation of presynaptic membrane function (82,83), and GABAergic function (74,84). By far the most well studied and replicated data deal with genes involved in oligodendrocyte and myelin-related functions. Hakak et al. (74), using mostly elderly schizophrenic and matched control DLPFC homogenates, showed downregulation of five 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. (73), using area 9 homogenates from the Stanley Brain collection showed significant downregulation in several myelin and oligodendrocyte related genes, such as proteolipid protein 1 (86), myelin associated glycoprotein (*MAG*), oligodendrocyte-specific protein *CLDN11*, myelin oligodendrocyte glycoprotein (*MOG*), myelin basic protein (*MBP*), neuroregulin receptor *ERBB3*, *transferrin*, *olig 1*, *olig 2*, and Sry Box10 (*SOX-10*) (73). Mirnics et al. (82) showed downregulation of genes involved in presynaptic function in the PFC, such as methyl maleimide-sensitive factor, synapsin II, synaptojanin 1, and synaptotagmin 5. Vawter et al. (83) showed downregulation of histidine triad nucleotide-binding protein and ubiquitin-conjugating enzyme *E2N*. Another important family of genes involved in schizophrenia is genes involved in glutamate and GABAergic function. Hakak et al. (74) showed an upregulation of several genes involved in GABA transmission, such as *GAD65* and *GAD67*. However, several reports have shown decreases in these proteins in schizophrenia (44, 87, 88). Hashimoto et al. (84) showed a downregulation of Parvalbumin gene, and Vawter et al. (83) showed downregulation of glutamate receptor *AMPA 2*. Another gene family of import in schizophrenia deals with signal transduction. Hakak et al. (74) showed upregulation of several postsynaptic signal transduction pathways known to be regulated by dopamine, consistent with the dopamine hypothesis of schizophrenia (85, 89), such as protein kinase A R II and NT-related protein 2. In a similar vein, Mirnics et al. (80) also showed downregulation of the *RGS4* gene in the PFC of patients with schizophrenia. Finally, Chung et al. (81) showed upregulation of the heat shock 70 gene in schizophrenic brain (81).

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 (90–92). However, there is also a robust collection of reports indicating that environmental factors, especially viral infections, can increase the risk for development of schizophrenia (93, 94). Emil Kraepelin (95) referred to potential for infections causing some forms of dementia praecox (schizophrenia) during early stages of brain development. Meninger (96) described 67 cases of schizophrenia in a large cohort of patients who contracted influenza during the pandemic of 1919. Later, Hare et al. (97) and Machon et al. (98) reported on an 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 a 5 to 15% excess of schizophrenic births in the

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; ↓ in dentate gyrus
	Synaptophysin	↓ in PFC 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 DLPFC
Regulation of neurotransmitter signaling	RGS4	↓ in PFC, 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
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

SNP, single nucleotide polymorphism; VCFS, velocardiofacial syndrome. From Meltzer and Fatemi, 2000 (7); Sullivan et al., 2006 (12).

Northern Hemisphere occurs during the months of January and March (92, 99, 100). This excess winter birth has not been shown to be caused by unusual patterns of conception in mothers or to a methodological artifact (92, 101). Machon et al. (98) and Mednick et al. (102) 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, 9 of 15 studies performed replicated Mednick's findings of a positive association between prenatal influenza exposure and schizophrenia (49). These association studies showed that exposure during the 4th to 7th months of gestation affords a window of opportunity for influenza virus to cause its teratogenic effects on the embryonic brain (103). Additionally, three out of five cohort and case–control studies support a positive association between schizophrenia and maternal exposure to influenza prenatally (104–106). Subsequent studies have now shown that other viruses, such as rubella (107), may also increase the risk for development of schizophrenia in the affected progeny of exposed mothers (92, 107). By far, the most exciting evidence linking viral exposure to development of schizophrenia was published recently by Karlsson et al. (94), who provided data suggestive of a possible role for retroviruses in the pathogenesis of schizophrenia (93). Karlsson and colleagues (94) identified nucleotide sequences homologous to retroviral polymerase genes in the 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 healthy subjects (93, 94). 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 (93). 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. (93), 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 (93).

At least two mechanisms may be responsible for transmission of viral effects from the mother to the fetus: 1) **Via direct viral infection.** There are clinical, as well as direct experimental reports (108–111) 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 (110). Additionally, Aronsson et al. (110) demonstrated that 10 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 the *NS1* gene is known to play a regulatory role in the host–cell metabolism (112). Several in vitro studies have also shown the ability of human influenza A virus to infect Schwann cells (113), astrocytes, microglial cells, and neurons (108), and hippocampal GABAergic cells (114, 115), selectively causing persistent infection of target cells in the brain. 2) **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 (116–120). New reports show the presence of serologic evidence of maternal exposure to influenza as causing increased risk of schizophrenia in offspring (50). 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 (IL)-1β, IL-6, and tumor necrosis factor (TNF)-α are elevated in pregnant mothers after maternal infection (116, 117, 120) and after infection in animal models (118, 119). All of these cytokines are known to regulate normal brain development and have been implicated in abnormal corticogenesis (121–123). Additionally, expression of messenger RNAs (mRNAs) for cytokines in the CNS is developmentally regulated both in man and in mouse (124–128), emphasizing the significant role that cytokines play during neurodevelopment. IL-1β, IL-6 and TNFα cross the placenta and are synthesized by mother (129), by the placenta (130), and by the fetus (120). 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 (50, 131). 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 (132), or, after maternal exposure to *Escherichia coli* cell wall endotoxin lipopolysaccharide, cause disruption of sensorimotor gating in the offspring (133). Finally, maternal exposure to poly I:C also causes disrupted latent inhibition in rats (134). 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 (92, 131), Rh factor incompatibility (136), and autoimmunity caused by infectious agents (137).

TABLE 6.5. Neurologic soft signs.

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

FIGURE 6.5. Abnormalities of left-hand posture in preschizophrenic children (reprinted with permission from the Schizophrenia Bulletin (140)).

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 in patients with schizophrenia, indicating a second trimester event (138). Multiple reports indicate the presence of premorbid neurologic soft signs (Table 6.5) in children who later develop schizophrenia (139, 140). Slight posturing of hands and transient choreoathetoid movements has been observed during the first 2 years of life in children who later developed schizophrenia (Fig. 6.5) (140, 141). 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 (142, 143). All of these findings are consistent with schizophrenia as a syndrome of abnormal brain development.

6. Clinical Findings

6.1. Clinical Signs and Symptoms of Schizophrenia

The current diagnostic criteria adopted by DSM-IV-TR is based on extensive research dating back to initial findings of Kraepelin, Bleuler, and Schneider (5, 8, 144). Unlike other medical conditions, no one sign is diagnostic of schizophrenia (7). Thus, it is absolutely important to obtain as much clinical history regarding the patient to help establish a correct diagnosis.

As mentioned earlier, The DSM-IV-TR criteria consist of six major topics:

1. *Criterion A* includes 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, 29). 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 (29). Hallucinations are abnormal perceptions of sensory experiences that 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) (7,145). 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, 29). Command auditory hallucinations may lead the patient to act on the command to harm self or others. Disorganized speech and behavior reflect underlying thought disorder or impairment (7, 29). Examples of abnormal speech include circumstantiality, tangentiality, derailment, illogicality, incoherence, concrete speech, clanging, neologisms, echolalia, thought blocking, perseverations, and poverty of content (7, 29). 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 (29). 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, 29). These negative symptoms reflect endogenous markers of schizophrenia and are, thus, called primary negative symptoms (29). Negative symptoms such as depression or demoralization, which may be caused by side effects of medications, are called secondary negative symptoms (29).
2. *Criterion B* reflects significant social/occupational dysfunction, because the onset of disease is such that patient is not able to work, go to school, provide self-care, and relate to others normally.
3. *Criterion C* reflects the continuous presence of illness for at least 6 months. This 6-month period must include 1 month of Criterion A (active-phase symptoms), and may include prodromal or residual symptoms. The prodromal symptoms predate the active phase of psychosis and consist of symptoms of impending social withdrawal, restricted range of affect, cognitive difficulties, and increasing emergence of odd behavior (29). The residual phase of the disease reflects presence of attenuated forms of positive or negative symptoms.
4. *Criterion D.* Presence of mood disorders or schizoaffective disorder has been excluded.
5. *Criterion E.* The schizophrenic symptoms are not caused by various medical conditions or by direct physiological effects of a drug of abuse.
6. *Criterion F.* In the presence of autism or another pervasive developmental disorder, a diagnosis of schizophrenia is made based on the presence of prominent delusions or hallucinations for at least 1 month.

6.2. Mental Status Examination in a Subject with Schizophrenia

6.2.1. Appearance

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

6.2.2. Affect

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

6.2.3. Mood

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

6.2.4. Speech

Evaluation of patient's speech may identify presence of loose, illogical, or bizarre thought patterns. Additionally, patients may exhibit various abnormalities of speech, such as tangentiality, circumstantiality, neologisms, clang association (speech directed by the sound of a word rather than by its meaning) (145), perseveration, and poverty of content (7). Patients may also express echolalia or thought blocking. Evidence of tardive dyskinesia or dystonia affecting a patient's speech should be investigated.

6.2.5. Thought Form and Content

Thought form can be ascertained while listening to patient's speech. Thus, presence of a 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 a 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 the patient for the presence of depression, mania, anxiety, panic, racing thoughts, irritability, suicidal and homicidal ideations, or plans or histories of suicide or violence toward others. Presence of obsessive–compulsive symptoms, past or recent histories of traumatic events, and signs of posttraumatic stress disorder (PTSD) should be evaluated.

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, the specifics of the sex of voices heard, the loudness, and the origin of voices emanating from inside or outside the patient's head should be investigated. The presence of command auditory hallucinations that may order patients to harm themselves or others should be ascertained. The form and color of visual hallucinations should be evaluated. Visual hallucinations occurring during sleep, before, or immediately after sleep are not necessarily indicative of a pathological process.

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 present major abnormalities, either through bedside examination or by performance of a neuropsychological battery of tests. Insight and judgement are generally evaluated by questioning a 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 a patient's degree of abstraction or concreteness of thought. Most schizophrenic patients exhibit IQ scores 10 points lower than the general public and exhibit impairments in attention, working memory, visual spatial memory, semantic memory, recall memory, and executive functions (7). The presence of cognitive abnormalities in schizophrenia seems to be independent of positive, negative, or disorganization symptoms (7).

6.2.8. Physical Examination

As in all other fields of medicine, every psychiatrist must be able to perform a focused physical examination to identify the presence of any general medical or neurologic abnormalities. However, because of potential boundary issues, the 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. The 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 caused by atypical agents, it would be judicious to obtain baseline and follow-up weight, vital signs, and waist circumference (body mass index) for every patient examined (146).

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), the Brief Assessment of Cognition in Schizophrenia (BACS) (147), and the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) (148) can identify various brain abnormalities and should be performed in all initial evaluations.

6.2.10. Laboratory Investigations

6.2.10.1. Blood, Urine, and CSF

Although no specific blood, urine, or CSF tests are available to demonstrate the presence of schizophrenia unequivocally, performance of certain blood and urine tests to exclude the presence of nonpsychiatric causes for psychotic symptoms is warranted in all initial examinations. Tests such as thyroid function (thyroid-stimulating hormone [TSH], T_3, T_4), rapid plasma reagin [RPR], HIV, fasting lipid panel, complete blood count with differential, metabolic panel (electrolytes, liver enzymes, blood urea nitrogen [BUN], glucose, and creatinine), erythrocyte sedimentation rate (ESR), antinuclear antibody (ANA), rheumatoid factor (RF), B12, folate, prolactin, urinalysis, urine tox screen, blood alcohol level, and baseline electrocardiogram (ECG) should be performed during the initial evaluation, as warranted by clinical judgment of the examining psychiatrists. Evaluation of hemoglobin A1C to exclude the 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 for a lumbar puncture is warranted.

6.2.10.2. Brain Imaging

Ventricular enlargement and increased brain sulcal prominence can be identified in computed tomography (CT) or MRI views. Although these 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 schizophrenia, none are diagnostic of schizophrenia (7). More recently, DTI has shown the presence of white matter tract abnormalities in schizophrenic patients, but, again, these findings have yet to be fully replicated (149).

6.2.10.3. Functional Brain Imaging

Use of functional MRI (fMRI), single-photon emission computed tomography (SPECT), and positron emission tomography (PET) scanning has provided a wealth of information regarding various brain function abnormalities in schizophrenia (150–153). These abnormalities include dysfunction of information storage and retrieval by the DLPFC, abnormal inhibitory response to sensory stimuli by the anterior cingulate cortex, abnormal encoding and retrieval of memory by the hippocampus, abnormal reception and integration of sensory information by the thalamic nuclei, primary sensory cortices, and the multimodal cortices, and impaired performance of cognitive tasks by the basal ganglia, thalamus, and cerebellum (29, 154–157). Very recently, Hubl et al. (158) showed that abnormal activation of the primary auditory cortex in schizophrenic subjects may be a biological cause for the production of auditory hallucination.

6.3. Differential Diagnosis

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

6.3.1. Mood Disorders

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

6.3.2. Psychotic Disorders Caused by 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 nonschizophrenic psychosis. Many substances can cause psychosis, such as amphetamines, substituted amphetamines (ecstacy), 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, Creutzfeldt–Jakob 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 examinations will help the psychiatrist in identifying the cause of psychotic symptoms and excluding schizophrenia (7).

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 the 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 6 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.

6.3.4. Other Axis I Disorders

Symptoms that may resemble hallucinations or paranoia may be observed in PTSD patients but these ensue after a traumatic event. Severe intrusive thoughts in obsessive–compulsive disorder (OCD) patients neither reach the level of delusionality seen in schizophrenia or, if they occur in absence of insight, do not accompany the functional incapacity seen in psychotic patients. Finally, in subjects with hypochondriasis or body dysmorphic disorder, no hallucinations or delusions are present (29).

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.

7. Pharmacological Treatments of Schizophrenia

7.1. Clozapine

Clozapine is a dibenzodiazepine and the prototype for most of the atypical antipsychotics (agents that 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, exhibit greater 5HT2 than D2 receptor antagonism, and do not cause hyperprolactinemia (155, 156)). Clozapine has a complex pharmacologic profile encompassing affinities for 5HT2A, 5HT2C, 5HT6, 5HT7, α_1 and α_2 adrenergic, M1 muscarinic, and histaminergic receptors (7). Clozapine exhibits inverse agonist activity at 5H2A and 5HT2C receptors, blocking constitutive activity of these receptors (29). The ratio of 5HT2A to D2 receptor affinities may signal the low EPS profile of clozapine (7).

Clozapine has been shown to be effective in treatment-resistant schizophrenia (159). This important study compared the efficacy of clozapine with chlorpromazine in 268 subjects with treatment-resistant schizophrenia (defined as having failed to respond to at least three previous antipsychotics). By 6 weeks, 30% of the clozapine-treated group but only 4% of the chlorpromazine-treated group responded to the respective medications (17, 159). Thus, clozapine remains the only antipsychotic agent to date that is US Food and Drug Administration (FDA)-approved for treatment-resistant schizophrenia (160). Additionally, other studies have shown superiority of clozapine versus typical agents in the treatment of total psychopathology, EPS, and tardive dyskinesia and categorical response to treatment (160). Clozapine reduces positive, negative, and cognitive symptoms of schizophrenia without causation of EPS, tardive dyskinesia, or hyperprolactinemia (29). Additionally, clozapine has been shown to reduce depression and suicidality (7, 29).

The dose range of clozapine varies from 150 to 600 mg/day for most patients (7). The initial dose of 25 mg/day must be titrated upward slowly (increments of 25 mg every 3 days) because of hypotensive and tachycardic side effects (7). The average dose is approximately 400 to 500 mg/day as a twice daily regimen (7). Plasma levels of 350 to 400 ng/ml have been associated with good clinical response (7).

Despite clozapine's important clinical efficacy, several side effects must be considered as potentially significant and life threatening. Agranulocytosis occurs within the initial 4 to 18 weeks of treatment, necessitating monitoring of white blood cell (WBC) and neutrophil count every 2 weeks for the first 6 months (29), every 2 weeks for the next 6 months, and once monthly thereafter (7). If the WBC count falls below 3,000 cells/mm^3 or the absolute neutrophil count below 1,500 cells/mm^3, clozapine administration must be stopped. On diagnosis of agranulocytosis, administration of granulocyte colony stimulating factor (G-CSF) and hospitalization is warranted. The death rate from agranulocytosis is approximately 1 per 10,000 patients (29). 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, leukocytosis, eosinophilia, and fever (7). Seizures can be treated with valproic acid or lamotrigine supplementation (161, 162).

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 the USA. Several studies suggest that risperidone may be more effective than typical antipsychotics in acute and maintenance treatment of schizophrenic subjects (160). Although 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 (160).

The recommended dosage of risperidone is 2 to 8 mg/day (9). Risperidone causes higher occupancy of D2 receptors than does clozapine and may cause mild EPS even at a 2 to 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.

7.3. Olanzapine

Olanzapine is a thienobenzodiazepine agent and the third FDA-approved atypical agent, marketed in the USA in the late 1990s. This novel agent exhibits nanomolar affinity at several receptor sites, including D1–D4, 5HT2, 5HT3, 5HT6, muscarinic M1–5, α1 adrenergic, and H1 histaminergic sites (7). Additional novel findings show that olanzapine causes modulation of several important brain genes such as Reelin, insulin, RGS2, pyruvate kinase, calbindin, and homer 1 after chronic administration in rats (163). 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 (164). Olanzapine also downregulates the soluble isoform of COMT in the frontal cortex of rats, helping upregulate the levels of dopamine in this important brain area (180).

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 (160) and in treatment of refractory patients. The dose range for olanzapine is 10 to 30 mg/day. 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).

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 a moderate affinity for D2 and a low affinity for M1 muscarinic receptors (7). The dose range of quetiapine is 300 to 800 mg/day, with similar efficacy to typical agents. Quetiapine is associated with low EPS propensity and low prolactin elevation (160). The most common side effects include sedation, dry mouth, agitation, constipation, and orthostatic hypotension (7).

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, and is associated with minimal weight gain, sedation, or prolactin elevation (160). The dose range is 120 to 200 mg/day. Despite initial concerns for ziprasidone causing QT-interval changes, such as torsade de pointes, the FDA does not require ECG acquisition before treatment and no published reports indicate any cardiotoxic effects (160).

7.6. Aripiprazole

Aripiprazole is the first FDA-approved partial dopamine D2 agonist, marketed in 2002, with partial agonist activity at the 5HT1A receptor and 5HT2A antagonism (29, 160). Aripiprazole has low EPS propensity, and a low liability for hyperprolactinemia and weight gain (160). The dose range is 10 to 30 mg/day (29). Aripiprazole is effective in short- and long-term treatment of schizophrenia (160). Side effects may include activation and nausea (29).

7.7. Paliperidone

The newest atypical agent, approved by FDA in 2007, is paliperidone, which is a major metabolite of risperidone with pharmacological activity at monoamine receptors analogous to risperidone (165). The terminal half-life is less than 24 hours (165). Paliperidone does not undergo significant hepatic metabolism and has a dose range of 3 to 15 mg/day once daily (165). A recent study (165) shows efficacy and safety of paliperidone-ER in an acute and a 14-week trial treatment of schizophrenia (165).

7.8. Typical Antipsychotics

Results of CATIE trials (166) indicated that there may not be significant differences between several atypical agents (clozapine, olanzapine, ziprasidone, aripiprazole, and risperidone) and a typical agent (perphenazine) regarding efficacy in treatment of schizophrenic positive symptoms. Indeed, introduction of chlorpromazine and later antipsychotic agents such as haloperidol in the 1950s revolutionized the treatment of schizophrenia (7). These agents clearly treated positive symptoms in 60 to 70% of patients and enabled many patients to leave hospitals for the first time in decades. The early hypotheses suggested that the actions of typical antipsychotics in ameliorating the positive symptoms of schizophrenia were caused by 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 chronic

upregulation or repression may lead to stabilization of positive, negative, and cognitive deficits in schizophrenia (163, 164,167–170). Thus, it seems 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.

7.9. Multiple Phases of Pharmacologic Treatment

In the acute phase treatment, patients with florid psychotic symptoms are generally admitted to a hospital setting and given short-acting antipsychotic agents (ziprasidone, olanzapine, or haloperidol) alone or in combination with benzodiazepines and/or anticholinergics. The clinical decision to begin antipsychotic treatment is dependent on several factors, including side effect profile, history of response to medications, and patient preference (Table 6.6). The order of antipsychotic agents of choice based on low propensity for metabolic side effects, EPS, and tardive dyskinesia may be aripiprazole, quetiapine, risperidone/paliperidone, ziprasidone, olanzapine, and haloperidol. In cases of noncompliance, depot medications, such as long-acting risperidone, haloperidol, or fluphenazine may be administered (29).

In the continuation-phase treatment, the patient's response to the antipsychotic agent, and the side effect profile, tolerability, and compliance will be monitored carefully (29). It is generally expected that optimal response to most agents will be achieved by 4 to 6 weeks, however, longer periods of therapy may be necessary in certain individuals. In some patients, residual constellations 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.

In the maintenance-phase treatment, patients who have responded well to various agents should be treated indefinitely to prevent relapse and worsening of the disease process. In treatment-refractory cases, clozapine seems to be the only drug with proven efficacy (29).

TABLE 6.6. Commonly used antipsychotic drugs.

Class and drug name	Dosage range (mg)	Chlorpromazine equivalents (mg/day)	Parenteral dosage	Galenic forms[a]
Typical drugs				
Chlorpromazine	300–1000	100	25–50 mg	O, L, I, S
Fluphenazine	5–20	2	1.25–2.25 mg	O, L, I
Fluphenazine decanoate	—	—	12.5–50 mg every 1–4 weeks	—
Fluphenazine enanthate	—	—	12.5–50 mg every 1–4 weeks	—
Haloperidol	5–20	2	5–10 mg	O, L, I
Haloperidol decanoate	—	—	25–100 mg every 1–4 weeks	—
Loxapine	30–100	10	25 mg	O, L, I
Mesoridazine	150–400	50	25 mg	O, L, I
Molindone	30–100	10	NA	O, L
Perphenazine	16–64	10	5–10 mg	O, L, I
Pimozide	0.5–2	2	NA	O
Thioridazine	300–800	100	NA	O, L
Thiothixene	15–50	5	2–4 mg	O, L, I
Trifluoperazine	15–50	5	1–2 mg	O, L, I
Atypical drugs				
Aripiprazole	10–30	4[b]	NA	O, L
Clozapine	150–600	50–100[b]	NA	O
Olanzapine	10–30	4	NA	O, I, OD
Paliperidone	3–15	NA	NA	O
Quetiapine	300–800	100	NA	O
Risperidone	2–8	1	NA	O, L, I, OD
Risperidone microspheres	—	—	25–50 mg every 2 weeks	—
Ziprasidone	120–200	40	10 mg	O, L, I

O, oral; L, liquid; I, injection; S, suppository; OD, oral disintegrating form. Meltzer et al., 2008 (29). Adapted with permission from the International Psychopharmacology Algorithm Project (IPAP) algorithm for the treatment of schizophrenia, available at www.ipap.org.

[a]Meltzer and Fatemi, 2000 (7).

[b]Drug Information Handbook for Psychiatry, 6th ed. Fuller MA, Sajatovic M, eds. Lexi-Comp, 2007 (175).

8. Antipsychotic-Related Side Effects

One of the major reasons for the choice of new second-generation antipsychotics relates to the high frequency of several side effects that are more prevalent with typical agents. For example, EPS, such as dystonias (repetitive involuntary skeletal muscle contractions [Fig. 6.7]), dyskinesias (slow or tardive dyskinesias or severe involuntary choreiform, athetoid, or rhythmic muscular contractions that may involve the face, neck, tongue, hands, trunk, and legs (Fig. 6.6)), pseudoparkinsonism, rabbit syndrome, and akathisias occur secondary to the use of high-potency typical antipsychotics. All of these side effects, except for tardive dyskinesia, can be treated by judicious use of anticholinergics, benzodiazepines, or propranolol, or by reduction in dose of the antipsychotic agents or by switching to an atypical agent. There are no proven treatments for tardive dyskinesia. Nonneurologic side effects may include hyperprolactinemia, gynecomastia, impotence, amenorrhea, weight gain, hematologic effects, jaundice, and cardiac effects (7).

9. ECT 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 the current literature (7).

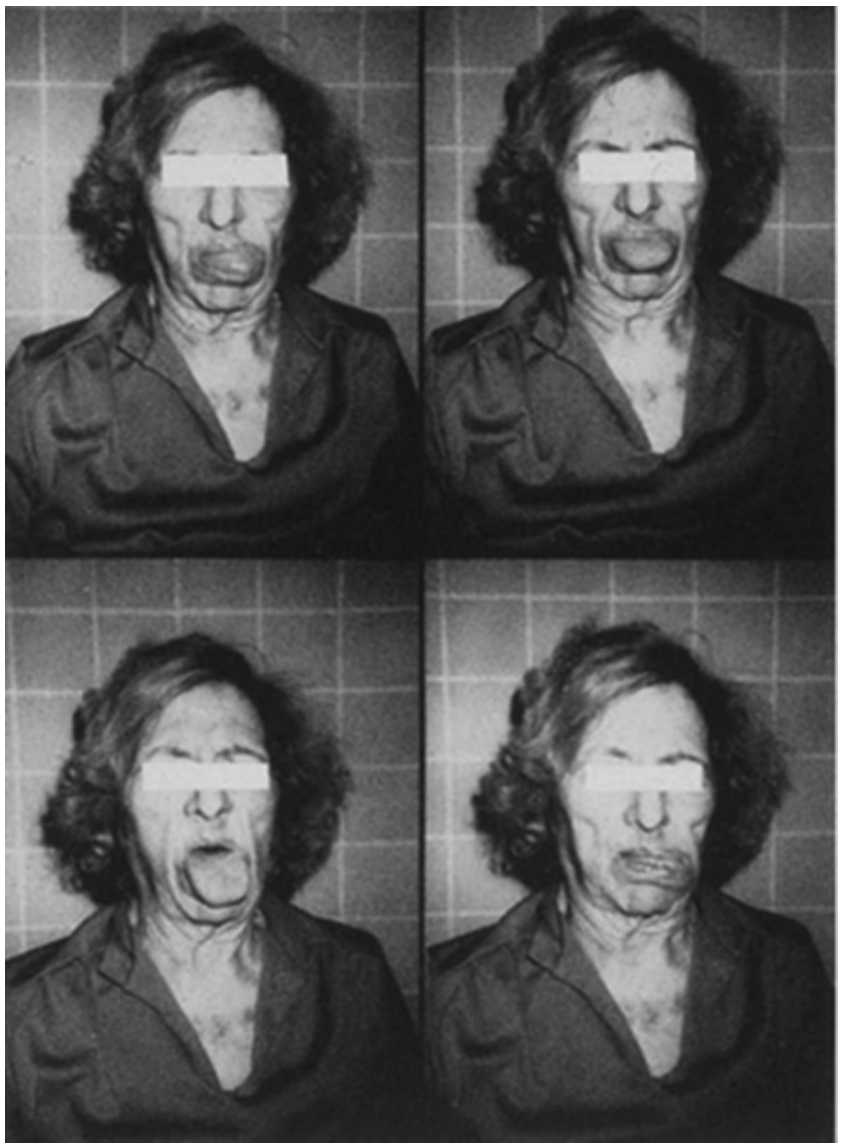

FIGURE 6.6. A psychotic woman treated with numerous neuroleptic drugs for at least 15 years developed typical orofacial–buccolingual tardive dyskinesia (reprinted with permission from Blackwell Scientific Publications (178)).

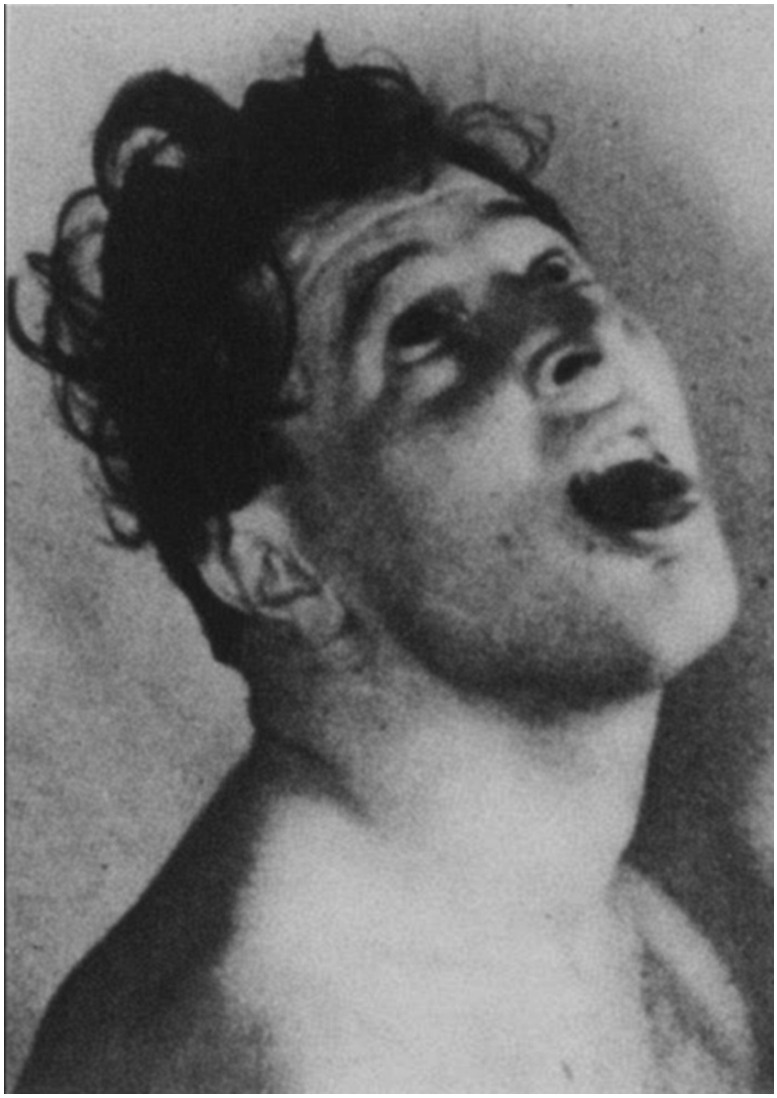

FIGURE 6.7. OCG with torticollis and tongue protrusion (reprinted with permission from Blackwell Scientific Publications (178)).

10. Psychosocial Treatment

Several psychosocial treatment modalities, such as cognitive–behavioral therapy, personal therapy, compliance therapy, acceptance and commitment therapy, as well as supportive psychotherapy, 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 (29). 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 the medication regimen (29).

11. Time Course of Schizophrenia

Disease onset is highly variable. The prodromal phase consists of a period during which the patient may experience social withdrawal, decreased motivation, poor cognition, increasing odd behavior, and restricted affective range (29). During the active phase (first psychotic break), patients exhibits florid psychotic symptoms either in response to life stressors or after substance abuse (29). In the residual phase, some schizophrenic symptoms remain that persist despite treatment.

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.

TABLE 6.7. Predictors of course and outcome in schizophrenia.

Factor	Good outcome	Poor outcome
Age at onset[1]	Approximately 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 before 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

Key: 1, clinical; 2, diagnosis; 3, environment; 4, treatment; 5, genetic. Meltzer and Fatemi, 2000 (7); Meltzer et al., 2008 (29); Perkins et al., 2006 (171).

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, the 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.

Results from several long-term reports studying outcome in schizophrenia show that, during a 15-year period, several disease courses may emerge: 1) 9 to 38% of patients will have a sustained recovery (171); 2) 10% of the patients will have a persistent unremitting course (171–173); 3) 67% of patients will have a good outcome (171, 174); 4) 32% of patients will have a poor outcome (171, 174); and 5) 10% will die by suicide (171). 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 women, breast cancer) (171).

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7
Schizoaffective and Schizophreniform Disorders

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

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

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 caused, in part, by the conceptual difficulty inherent in any intermediate or boundary category, and in part by a series of shifts in the term's definition that have occurred 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 or by a history of mood-incongruent psychotic features "in the absence of" or "to the relative exclusion of" affective symptoms. The RDC definition has been used in more studies of schizoaffective disorder than any other single, operational definition. Yet it was supplanted, at least in the official American nomenclature, when the *Diagnostic and Statistical Manual*, 3rd edition (DSM-III) assigned this term to a residual category for those who did not meet criteria for schizophrenia or a mood disorder but who seemed 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-IIIR 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 International Classification of Diseases, 10th revision (ICD-10), published in 1992, used the term for diagnostically ambiguous cases in which symptoms of both a mood disorder and schizophrenia were prominent, but not for cases in which an affective syndrome was simply accompanied by mood-incongruent psychotic features.

These circumstances recommend a generic use of the term *schizoaffective disorder* in any broad overview of the topic. Thus, this chapter applies 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 requires attention to the definition of schizoaffective disorder used in that study.

2. Etiology

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

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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 mood disorder 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 mood disorder probands; 2) if schizoaffective probands have simply a variant of schizophrenia, as is implied by the listing of schizoaffective disorder under schizophrenia in both ICD-10 and DSM-IV, 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 that this condition is, likewise, familial.

Table 7.1 summarizes the informative studies published in English during the past 20 years. Because schizophrenia-like symptoms may have different implications when they coexist with depressive syndromes than when they coexist with manic syndromes (5–8), this review summarizes studies in three groups: those that isolated schizoaffective manic patients, those that isolated schizoaffective depressive patients, and those that did neither. The intent of this display is to reveal overall patterns in group relationships. Many pairwise comparisons were statistically significant, but this information was 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 are comprised 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 ten of ten studies, relatives of schizoaffective probands were more likely to have schizophrenia than were relatives of mood disorder probands. The same was true in six of the seven studies that considered schizoaffective depression apart. Some earlier studies of schizoaffective mania supported the first hypothesis (4, 9–11), but later studies (12–14) showed patterns in line with those found in studies of schizoaffective depression.

Although fewer studies included schizophrenia cohorts for a comparison, they are consistent in finding 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, as well as the regular predominance of mood disorder in the families of mood disorder probands, argues against a spectrum hypothesis. Moreover, those few studies that have included healthy control probands have generally shown no increase in mood disorder within families of schizophrenic probands (15–17), nor any increase in schizophrenia within the families of mood disorder probands (15–17).

Studies of twins and of sibling pairs offer another way to investigate schizoaffective disorder. If most schizoaffective cases result from a "third psychosis," there should be few affected twins or sibling pairs in which one member has schizoaffective disorder and the other has schizophrenia or mood disorder. An early study, in fact, did find a 100% concordance for schizoaffective disorder (31). The members of these twin pairs were not assessed by separate raters, however. In contrast, Tsuang (32) conducted blind assessments of sibling-pair members. 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 than were the schizoaffective siblings with schizophrenic co-siblings. These findings are very consistent with a fifth hypothesis, that some schizoaffective patients are genotypically schizophrenic whereas others comprise genotypes for mood disorder.

Likewise, Cardno et al (33) described twin-pairs of individuals with schizophrenia, schizoaffective disorder, or manic disorder. Of the 32 pairs 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 disorder in 9 (28.1%). Model fitting indicated that the genetic liability to the schizoaffective syndrome was "entirely shared in common with the other two syndromes."

Finally, Laursen et al. (34) 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 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

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 J, 1973 (18) (author's definition)			
No. of probands	254	73	–
MR% schizophrenia*	1.4	5.9	
MR% mood disorder	13.3	7.1	
MR% schizoaffective	0.7	3.8	
Tsuang et al, 1976 (19) (author's definition)			
No. of probands	325	85	200
% FH + for schizophrenia†	0.5	1.3	1.3
% FH + for mood disorder	8.3	7.6	3.1
Suslak et al., 1976 (20) (author's definition)			
No. of probands	37	10	–
MR% schizophrenia	0.9	4.0	
MR% mood disorder	12.5	6.5	
Tsuang et al., 1977 (21) (author's definition)			
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 (22) (author's definition)			
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 (23) (author's definition)			
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 (24) (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 (13) (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 (25) (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 (26) (RDC)			
No. of probands	1086	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 (27)			
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)			
Abrahms and Taylor, 1976 (9) (RDC)			
No. of probands	78	10	–
% FH + for schizophrenia	0	0	–
% FH + for affective disorder	14.1	13.9	–
Pope et al., 1980 (4) (RDC)			
No. of probands	34	52	41
% FH + for schizophrenia	0	0	9.8
% FH + for mood disorder	32.4	40.4	9.8

TABLE 7.1. (continued)

	Proband diagnosis		
	Mood disorder	Schizoaffective or equivalent	Schizophrenia
Rosenthal et al., 1980 (11) (RDC)			
No. of probands	28	25	–
MR% schizophrenia	0	0	–
MR% mood disorder	24.8	24.6	–
Bocchetta et al., 1990 (12) (RDC)			
No. of probands	65	56	–
MR% schizophrenia	0.2	0.8	–
MR% mood disorder	9.1	4.2	–
MR% schizoaffective	1.3	3.4	–
Schizoaffective depression vs. depression (vs. schizophrenia)			
Coryell et al., 1982 (28) (DSM-III)			
No. of probands	221	95	235
MR% schizophrenia	0.5	1.6	2.8
MR% mood disorder	13.0	8.2	5.8
Abrams and Taylor, 1983 (29) (DSM-III)			
No. of probands	14	17	31
MR% schizophrenia	0	0	1.6
MR% mood disorder	12.9	19.3	6.8
Endicott et al., 1986 (30) (RDC)			
No. of probands	275	23	–
MR% schizophrenia	0	3.0	–
MR% mood disorder	35.9	25.2	–
MR% schizoaffective	0.3	1.0	–
Gershon et al., 1988 (13) (RDC)			
No. of probands	31	12	24
MR% schizophrenia	0	1.7	3.1
MR% mood disorder	19.6	19.5	16.0
MR% schizoaffective	0.7	3.4	0.6
Coryell and Zimmerman, 1988 (15) (RDC)			
No. of probands	29	47	21
MR% schizophrenia	0	2.3	1.4
MR% mood disorder	27.5	24.7	13.1
MR% schizoaffective	1.0	2.5	0
Bochetta et al., 1990 (12) (RDC)			
No. of probands	29	26	–
MR% schizophrenia	0	0.5	–
MR% mood disorder	3.3	3.7	–
MR% schizoaffective	0.4	0.5	–
Maj et al. 1991 (17) (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

*MR%, Morbid risk percent, the number of relatives with a disorder divided by the number of relatives at risk for that disorder; †% FH, family history positive, the number of probands with a family history of a disorder divided by the total number of probands.

predisposing alleles (35,36). Indeed, the results of the multiple family studies, together with those of twins and sibling pairs yield no clear support for any of them. Instead, the fifth "heterogeneity" or "diagnostic uncertainty" hypothesis seems to afford the best fit. Patients with this label may therefore 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 only 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.

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,

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 (24)		
No. of probands	28	22
MR% schizophrenia	4.1	0
MR% mood disorder	10.9	28.1
Kendler et al., 1986 (37)		
No. of probands	19	28
MR% schizophrenia	8.2	3.8
MR% mood disorder	7.3	14.5

MR, morbid risk.

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. At least two family studies clearly support this distinction (Table 7.2).

The DSM-IV concept 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 (17) 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. (37) and Maj et al. (17) provided values for healthy control subjects.

In comparison with those control subjects, RDC mainly schizophrenic probands (37) and DSM-IIIR schizoaffective probands (17) 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 (17, 37), although not significantly so, than the rates for healthy control subjects.

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 (38), such rates would have been widely disparate. The National Institute of Mental Health (NIMH) Epidemiologic Catchment Program (39) 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 (40) found a 0.4% lifetime prevalence for RDC schizoaffective disorder, whereas Vernon and Roberts (41) found a 0.8% prevalence. These figures were based on only three and four cases, respectively, however, and the individuals were not ill when interviewed.

Brockington and Leff (38) found 10 patients who met at least three of eight definitions for schizoaffective disorder from approximately 222 consecutive admissions; six patients (2.7%) met RDC criteria for schizoaffective disorder (one manic and five depressed). These figures are similar to those derived from all consecutive admissions seen during a several-year period; of 388 patients, 11 patients (2.8%) met RDC criteria for schizoaffective disorder (Coryell, unpublished data). In a subsequent series of 97 consecutively admitted nonmanic psychotic patients, 48.4% had RDC schizoaffective disorder, depressed type (42). In the same series, only 21 met RDC criteria for schizophrenia. Thus, although 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 (38), this chance coexistence should occur only once in a year in Great Britain, yet they found ten in 1 year in only three hospitals.

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 because these definitions vary so markedly (38), 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 (Table 7.3). 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. They may also exhibit euphoria, hyperactivity, recklessness, and grandiosity, as well as a blunted affect, bizarre

TABLE 7.3. Criteria for schizoaffective disorder.

RDC	DSM-IV
Period of illness with affective symptoms sufficient in number and duration for major depressive or manic episode PLUS At least one of the following: • Delusions of control • Delusions of thought broadcasting, insertion or withdrawal • Persistent non-affective hallucinations • Auditory hallucinations of running commentary or conversation • ≥1 week with delusions or hallucinations without prominent depressive or manic symptoms • If affective syndrome is depressive, definite instances of formal thought disorder with blunted or inappropriate affect, delusions or hallucinations, or grossly disorganized behavior PLUS Minimum duration of 1 week PLUS Affective syndrome overlaps	Period of illness with affective symptoms sufficient in number and duration for major depressive or manic episode PLUS At least two of the following: • Delusions • Hallucinations • Disorganized speech • Grossly disorganized speech or catatonic behavior • Negative symptoms OR At least one of the following: • Bizarre delusions or hallucinations • Auditory hallucinations of running commentary or conversation PLUS > 2 weeks of delusions or hallucinations in absence of prominent mood symptoms

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.

Phenomenologic 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 (42). 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 the non-endogenous depressive symptoms. This difference in endogenous symptom severity also emerged in another sample (43). Thus, broadly defined, *schizoaffective depression* designates patients who, on average, 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 also support a "heterogeneity" hypothesis.

Because these patients suffer from 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 that 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 (44).

5. Clinical Course

The prognosis for schizoaffective disorder seems to be worse than that for mood disorder (Table 7.4), 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 seem to reflect important differences in how schizoaffective disorder was 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 that defined the latter disorder by the persistence of schizophrenia-like symptoms between affective episodes (46, 61–64). 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" (11).

Although it is clear that the occurrence of psychotic features outside of affective episodes portends greater long-term morbidity, so does the presence of psychotic features within the affective syndrome seem to predict poorer outcomes. This seems to be equally so whether psychotic features accompany manic or depressive syndromes (8). Among affectively ill individuals with psychotic features, the

TABLE 7.4. Course of illness among patients with schizoaffective, mood-incongruent, or atypical psychoses: comparisons to probands with affective disorder or schizophrenia.

Reference (definition of schizoaffective disorder used in study)	Mood disorder	Schizoaffective or equivalent	Schizophrenia
Schizoaffective disorder not divided by polarity			
Tsuang et al., 1976 (19) (author's definition)			
No. of patients	325	85	200
% recovered	58	44	8
Angst, 1980 (45) (author's definition)			
No. of patients	254	150	–
% with "full remission"	39	27	–
Himmelhoch et al., 1981 (46) (author's definition)			
No. of patients	409	34	–
"Improved within 2 months"	39.7	5.9	–
Moller et al., 1988 (47) (ICD)			
No. of patients	36	27	34
% with "favorable outcome"	84	78	65
Grossman et al., 1991 (48) (RDC)			
No. of patients	40	41	20
% with outcomes better than "very poor"	84	57	45
Schizoaffective disorder not divided by polarity			
Williams and McGlasham 1987 (49) (author's definition)			
No. of patients	63	68	163
% recovered/good outcome	43	22	14
Moller et al., 1988 (47) (RDC)			
No. of patients	36	27	34
% with outcome GAS <greater than>50	65	78	84
Moller et al., 2000 (50) (ICD-9)			
No. of patients	48	68	85
Mean maximum GAS			
Score in final year	7.5	69	60
Schizoaffective mania vs. mania (vs. schizophrenia)			
Brockington, Wainwright, and Kendell, 1980b (51) (author's definition)			
No. of patients	66	30	53
% recovered	94	77	34
Abrams and Taylor, 1976 (9) (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 (11) (RDC)			
No. of patients	28	25	–
Probability of remaining well at 16 weeks	70	86	–
van Praag and Nijo, 1984 (52) (RDC)			
No. of patients	21	10	19
% with "good" treatment responses after 6 weeks	62	40	5
Grossman et al., 1984 (53) (RDC)			
No. of patients	33	15	47
% with "good" overall functioning	33	13	9
Maj, 1985 (54) (RDC)			
No. of patients	16	17	–
Mean score (SD) on Strauss–Carpenter	13.7(2.6)	12.6(1.7)	–
Outcome Scale (16 = optimal score)			–
Coryell et al., 1990b (7) (RDC)			
No. of patients	56	14	–
% recovered from index episode	95	79	–
Marneros et al., 1990a (55) (author's definition)			
No. of patients	30	56	
% with "no difficulties"	66.7	46.4	
Tohen et al, 1992 (56) (DSM-III)			
No. of patients	24	30	
Median time in remission	33	8	

TABLE 7.4. (continued)

Reference (definition of schizoaffective disorder used in study)	Mood disorder	Schizoaffective or equivalent	Schizophrenia
Schizoaffective depression vs. depression (vs. schizophrenia)			
Brockington, Kendell, and Wainwright, 1980a (57) (author's definition)			
No. of patients	66	75	53
% recovered	94	69	34
Coryell et al., 1982 (28) (presence of MIPFs)			
No. of patients	149	43	171
% recovered during follow-up	57.1	32.6	7.0
Abrams et al., 1983 (29) (DSM-III)			
No. of patients	14	17	31
Mean % improvement	80.7	92.7	34.5
van Praag and Nijo, 1984 (52) (RDC)			
No. of patients	29	12	19
% with "good" treatment response after 6 weeks	69	50	5
Grossman et al., 1984 (53) (RDC)			
No. of patients	330	24	–
% with "good" overall functioning	38	8	9
Maj, 1985 (54) (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 (58) (RDC)			
No. of patients	29	46	20
% recovered during follow-up	59	39	10
Opjordsmoen, 1989 (59) (DSM-III)			
No. of patients	50	33	94
% "healthy" at follow-up	66	42	10
Coryell et al., 1990a (6) (RDC)			
No. of patients	73	30	
% recovered from index episode	89	73	
Marneros et al., 1990b (60) (author's definition)			
No. of patients	76	45	
% with "no difficulties at follow-up"	63	56	
Tsuang and Coryell 1993 (61) (DSM-III-R)			
No. of patients	32	11	22
% recovered	44	0	0
Coryell and Tsuang 1985 (43) (presence of MIPFs)			
No. of patients	101	89	219
% good outcomes (mental)	62	45	21

GAS, global assessment scale; FRS, first-rank symptoms; SD, standard deviation; MIPF, mood-incongruent psychotic features.

quality of those features has added prognostic importance. A review of 13 studies that compared mood-congruent and mood-incongruent psychotic features consistently showed at least a somewhat poorer outcome for patients with mood-incongruent features (65).

The heterogeneity that remains with groups with affective illness and mood-incongruent psychotic features has rarely been explored but may have further prognostic importance. Conus et al. (66) 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 score and greater negative symptoms, whereas 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 schizoaffective disorder. With one exception, lithium studies that have described five or more schizoaffective patients have reported poorer responses in that group than in more typically manic groups (Table 7.5). Subdivisions within schizoaffective groups are probably very meaningful to response prediction, but few studies have considered them. Maj (67) 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 because there are many shades of "response," "improved," and "recovered." In light of

TABLE 7.5. Outcome with lithium therapy in patients with schizoaffective (or equivalent) mania: comparisons with patients with manic disorder.

Reference (definition of schizoaffective disorder used in study)	Manic disorder	Schizoaffective mania
Schou et al., 1954 (68) (author's definition)		
No. of patients	30	8
% with "+ effect" acutely or prophylactically	40	25
Baastrup and Schou, 1967 (69) (author's definition)		
No. of patients	51	15
% reduction of no. of episodes with lithium	95	71
Zall et al., 1968 (64) (author's definition)		
No. of patients	33	10
% with "complete recovery"	79	10
Angst et al., 1970 (62) (WHO criteria)		
No. of patients	114	72
% with improvement in frequency of episodes with lithium	67	49
Aranoff and Epstein, 1970 (70) (author's definition)		
No. of patients	7	6
% with "unequivocal" acute response	71	33
Johnson, 1970 (63) (author's definition)		
No. of patients	19	11
% in "remission"	79	9
Prien et al., 1974 (71) (author's definition)		
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 (11) (RDC)		
No. of patients	27	15
Probability of remaining well after 16 wk	0.70	0.86
Yazici et al., 1999 (72) (presence of MIPFs)		
No. of patients	92	49
% good response	73	37
Maj et al., 1985 (54) (presence of MIPFs)		
No. of patients	63	16
% good response	52	19

WHO, World Health Organisation; MIPF, mood-incongruent psychotic features.

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. 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 to expect.

Additional findings from the NIMH 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% 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 patients 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 at intake, 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 without (or to the exclusion of) affective symptoms, poor adolescent friendship patterns, never married, and never manic. Few other studies have attempted to predict schizophrenia-like outcomes in such a sample. The most important of these yielded very similar results, however. Brockington et al. (57) 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 suggested a high level of specificity for psychotic depression, and it appeared to hold promise as a clinically useful diagnostic tool. Subsequent work has shown that nonsuppression rates among schizophrenic patients, although consistently lower than those for patients with psychotic depression,

are nevertheless higher than those for normal controls (73). It now seems 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 seems to be associated with relatively prominent negative features (74–77). 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 (78, 79) have found that, among such patients, nonsupression patients are substantially more likely to be free of psychotic features at the end of follow-up (1 and 8 years, respectively). The DST was not predictive in another follow-up study of schizoaffective disorder (80), but this sample included only four nonsuppressor patients and the analysis did not use persistent psychosis as an outcome measure.

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 (organic illness) and those that do not (functional illness). 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, several general features should increase the suspicion that psychiatric symptoms are arising from an organic 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 previous 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 (81). 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 history of similar symptoms not preceded by steroid ingestion, may, however, have a purely functional condition (81).

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 extreme 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 for 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 (82). This may be caused, in part, by 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 (83), and the syndromes can closely resemble their functional counterparts (84). In only 3 of the 69 cases described by Slater and Beard (84) 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. 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, both 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, because 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, whereas 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.

Largely on the basis of influential work by Spiker et al. (85), the pharmacotherapy of psychotic depression has been widely assumed to require a combination of an antidepressant and an antipsychotic. A recent meta-analysis used a uniform, intent-to-treat approach, and reached a more complex set of conclusions (86). In the combination of available studies, only a strong trend favored continued antidepressant and antipsychotic treatment over antidepressant monotherapy, although the combination was significantly more effective than antipsychotic monotherapy. Moreover, a combination of three available studies indicated a significant superiority of tricyclic antidepressant monotherapy over nontricyclic antidepressant monotherapy. Unfortunately, only one study has compared tricyclic monotherapy with placebo in psychotic depression (87).

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 will provide adequate protection against relapse. This will require careful surveillance, particularly in the first 6 months, when the risk of relapse is the highest (88). 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 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 do they simply require more time to develop the acceptance and habits necessary for adequate compliance? Because the options for effective prophylaxis are limited, it is important not to abandon a given drug prematurely. In addition, 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 hypomania (89).

8. Schizophreniform Disorder

Langfeldt coined the word schizophreniform in 1939 (90) to describe schizophrenia-like psychoses with relatively good prognoses. He intended this to be a heterogeneous group that would include "exogenically precipitated psychosis" (91). Indeed, the words schizophreniform and schizoaffective have been used interchangeably through much of the subsequent literature. The definitions found in DSM-III, DSM-IIIR, and DSM-IV are original, however; they separate schizophreniform disorder from schizophrenia solely based on a duration of less than 6 months, including the prodromal phase. The inclusion and exclusion criteria for DSM schizophreniform disorder and DSM schizophrenia are otherwise identical. DSM, thus, sets schizophreniform disorder apart both from mood disorder with mood-incongruent psychotic features and from schizoaffective disorder, and 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 common usage before DSM-III. This section is, therefore, restricted to studies using the DSM definitions.

Table 7.6 summarizes the studies that included comparisons with other diagnostic groups. Five of seven studies suggest that, similar to schizoaffective disorder, schizophreniform disorder defines an intermediate or heterogeneous group (42, 92–95). However, one found no difference between schizophrenia and schizophreniform disorder (96), whereas another concluded that schizophreniform disorder simply represented "atypical affective disorder" (97).

Consensus may not be forthcoming for several reasons. First, 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. Many acutely psychotic patients are unable to give valid accounts of such features in retrospect. Affective syndromes are also 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 regarding the true nature of schizophreniform disorder in a given case. As with schizoaffective disorder, the clinician should use all of 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 7.6. DSM-IIIR Schizophreniform disorder: studies of validity.

Study	No. with SF	Comparison groups	Design	Results
Helzer et al., 1981 (94)	7 (of 134 admissions with psychosis: 5.2%)	19 schizophrenia	Systematic follow-up averaging 6.5 years	SF patients had significantly better "combined social status score" and "outcome regression score"; less percentage of time in hospital; more manic symptoms
Coryell and Tsuang, 1982 (28)	93 (of 810 admissions studied: 11.5%)	86 bipolar MD; 203 unipolar MD; 214 schizophrenia	Chart follow-up averaging 3.1 years; family history study	16% of SF patients recovered versus 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 (96)	35 (of 128 with CT scans: 27.3%)	17 schizophrenia; 23 mood disorder; 27 other disorders; 26 neurologic controls	CT 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 (95)	21 (of 145 admissions: 14.5%)	76 unipolar MD; 10 bipolar MD; 24 other disorders; 14 schizophrenia	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 Tsuang, 1986 (58)	93	298 affective disorder 219 schizophrenia	Systematic follow-up of 40 years	SF patients were significantly more likely than MD patients, but only slightly less likely than schizophrenic patients, to be symptomatic at follow-up
Beiser et al., 1988 (92)	29 (of 575 patients with nonorganic psychosis: 4.5%)	60 schizophrenia; 73 affective disorder	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
Schimmelman et al., 2005 (98)	190	113 schizophrenia; 34 schizoaffective; 101 bipolar MD; 12 MDD;	Diagnostic stability over 18 month follow-up	Only 76 (40.0%) retained SF diagnosis; 100 (52.6%) re-diagnosed as schizophrenia
Fennig et al., 1994 (99)	11	57 schizophrenia; 13 schizoaffective	Diagnostic stability over 6 months follow-up	7 (63.6%) retained SF diagnosis; 3 (27.3%) re-diagnosed as schizophrenia

SF, schizophreniform disorder; MD, mood disorder; S, schizophrenia; MR, morbid risk; CT, computed tomography; DST, dexamethasone suppression test; TRH-ST, thyroid-releasing hormone stimulation test; MDD, major–depressive disorder.

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8
Delusional Disorders

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Abstract Delusional disorders are characterized by delusions in the absence of any other psychiatric illness that could account for the delusional thought processes. DSM-IV lists erotomanic, grandiose, jealous, persecutory, and somatic subtypes. The prevalence of delusional disorders has been estimated to be 24 to 30 cases per 100,000 people, and their annual incidence to be 0.7 to 3.0 new cases per 100,000 people. The available evidence does not suggest a shared predisposition with either schizophrenia or mood disorders. Although the neuropathology of delusional disorders is unknown, there is some evidence suggesting enlarged ventricles and eye-tracking abnormalities. The course of the illness is highly variable; some patients recover rapidly and completely but, in other patients, the illness 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 · Delusional parasitosis · Grandiose delusional disorder · Jealous delusional disorder · Persecutory delusional disorder

1. Definition

Delusions are among the most common psychotic symptoms. Forty-eight percent of manic patients and 33% 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 (*Diagnostic and Statistical 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 of their essential features by DSM-II (5) and in DSM-III (6) as Paranoia and Acute Paranoid Disorder.

Beginning with DSM-III-R and continuing in DSM-IV, 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, 8). The delusional disorders have been expanded to include persecutory, erotomanic, grandiose, jealous, and somatic types.

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* (9). No subtypes of delusional disorder are specified, but *Other Persistent Delusional Disorders* includes

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delusional dysmorphophobia, involutional paranoid state, and paranoia querulans.

Both DSM-IV and ICD-10 require delusions in the absence of schizophrenia, mood disorder, or a toxic, metabolic, or neurological disorder. DSM-IV requires a minimum duration of 1 month, and ICD-10 specifies that the delusions be present for a "few months." DSM-IV further specifies that the delusion is not bizarre, and 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 is no longer classified as a delusional disorder but as a separate psychotic disorder: *shared psychotic disorder* in DSM-IV and *induced psychotic disorder* in ICD-10.

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 because of their lack of insight. There are clear indications that delusions of parasitosis are not rare in dermatology clinics. For instance 20 of 415 subjects seeking cosmetic surgery were diagnosed with delusional disorders (10).

The literature provides a demographic picture of delusional disorder (Table 8.1) (11). The prevalence has been estimated to be 24 to 30 cases per 100,000 people. The annual incidence of delusional disorders was estimated at 0.7 to 3.0 new cases per 100,000 people. It accounts for 1.3% of all first admissions to psychiatric hospitals and 3.9% of first admissions for psychoses. Data from the 20-year period from 1932 to 1952 indicate that there was little change in the incidence over that time.

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 female patients, 55% of first admissions being women (11).

The demography in the elderly seems to mirror that in younger populations (12). The prevalence in a community sample of persons 65 years and older was estimated to be 40 cases per 100,000 people and the annual incidence to be 15.6 per 100,000 people. The apparent increase in incidence over the rate of 0.7 to 3.0 cited above may indicate an increased rate of new cases among the elderly, or it may be because the geriatric population was interviewed and, thus, more cases were detected. The geriatric incidence rate cited has a very wide confidence interval and, therefore, it should not be considered a stable estimate.

TABLE 8.1. Epidemiology of delusional disorders.

Incidence[a]	0.7–1.3
Prevalence[a]	24–30
Percent of first admissions[a]	1.3%
Mean age of onset[b]	39 years
Sex ratio (F/M)	1.18

The numbers for incidence, prevalence, and sex ratio represent cases per 100,000 people.
[a]From Kendler, 1982 (11).
[b]From Retterstol, 1966 (34).

3. Etiology and Pathophysiology

Delusional disorders have been a relatively neglected area of psychiatric research, and consequently, the literature on etiology is very limited. 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 (13) 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. Because 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) (14). The observations indicate that Kahlbaum's original concept of paranoid disorders, as uncommon but distinct entities, may be correct because they appear genetically distinct from the other psychoses. 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.

Although there is no evidence suggesting that delusional disorders overlap genetically with either mood or schizophrenic disorders, there is some evidence suggesting

TABLE 8.2. Family history in 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.

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 (Table 8.2) 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 blind diagnoses to them. 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, whereas 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 regarding the neurobiology of delusional disorders is available. A structural magnetic resonance imaging study found larger ventricles in late-onset delusional disorders compared with late-onset schizophrenia, both groups having larger ventricles than do healthy control subjects (15). A study of eye-tracking performance reported deficits in delusional disorders similar to those reported from other research on schizophrenia (16). Together, these studies do not suggest qualitative differences concerning the neurobiology of delusional disorders compared with that of schizophrenia, although there are insufficient data to draw any firm conclusions.

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 people 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 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, whereas 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 emphasizes that the quality of the delusions is not bizarre. Winokur (17) has proposed that the delusion be possible, even though implausible, as opposed to impossible, as a test criterion for being nonbizarre. This concept has been incorporated in DSM-IV, which considers delusions bizarre if they are "clearly implausible, not understandable, and not derived from ordinary life experiences" (8).

Many delusional disorders are accompanied by hallucinations that are not sufficiently prominent to justify a diagnosis of schizophrenia. Some would exclude any patient with hallucinations (17), whereas others would include them as long as the hallucinations are not prominent (18). DSM-IV and ICD-10 use the latter interpretation.

When a thought disorder is present, it is not prominent and does not affect communication, as does the thought disorder of schizophrenia. Winokur (17) 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. The clinician should always inquire about this area, given the potential consequences of these acts.

DSM-IV has outlined five subtypes that closely parallel those proposed by Monro (19). These are erotomanic, grandiose, jealous, persecutory, and somatic types. However, other delusional themes are consistent with a diagnosis of delusional disorder, as long as they meet the major defining criteria.

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.

5. Some Illustrative Cases

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, during 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. During 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.

Meyer suggested the following states in the development of paranoid symptomatology (20). 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.

5.2. Case History 2: Jealous Delusional Disorder

A 22-year-old college student 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. During 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 school performance was blamed on his wife for the anguish she was causing him. He was hospitalized after the incident with the hammer, and he 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*. Such patients become convinced that their spouses are unfaithful, and they become preoccupied with proving the infidelity and extracting a confession. Of all of the paranoid disorders, these patients spend the greatest amount of time attempting to verify their suspicious (21).

5.3. Case History 3: Erotomania

A 47-year-old woman was convinced that her supervisor was in love with her, because 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 regarding 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 psychoeducation. 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 they 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 deClerambault's syndrome and is now called erotomania in DSM-IV (22–24).

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 during 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 (25). 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, patients believe that they are infested with insects or other foreign bodies under the skin. Patients with delusional hypochondriasis believe that they are affected by a serious illness and characteristically visit multiple physicians as well as other healers. Patients with fixed beliefs regarding real or imagined defects in their appearance are diagnosed as having body dysmorphic disorder if the belief is not of delusional proportions, and this disorder is classified as a somatoform disorder in DSM-IV. However, if the belief is clearly delusional, they may receive the additional diagnosis of delusional disorder, somatic type.

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 (26). 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 disorders patients (see Sect. 8.5.3 above).

There are relatively few studies examining the issue of diagnostic stability over long periods. Available information suggests that, in a large proportion of subjects (probably $\sim$50%), the diagnosis of delusional disorders is confirmed at follow-up but also that a significant proportion receives another diagnosis, most often schizophrenia (27).

7. Differential Diagnosis

Because delusional disorders are uncommon, 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 (28).

Dementia may be accompanied by delusions and should be suspected in an elderly paranoid patient. 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, whereas 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 caused by 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), and 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 the delusions tend toward the bizarre, when the affect is blunted or inappropriate, 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 preexisting mood illness is present, or when the family history is positive for mood disorder. 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. Because 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. 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.

Hypochondriasis differs from somatic delusional disorder in that the somatic concern is not delusional. The hypochondriacal patient suspects an illness and cannot be reassured by negative examinations but lacks the certainty of belief that is characteristic of somatic delusional disorders. Hypochondriasis 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. Similarly, patients with excessive and unreasonable concerns regarding their physical appearance are classified as having body dysmorphic disorder, but, if the belief is delusional, they receive the additional diagnosis of somatic delusional disorder. It could be argued that, in the latter case, the diagnosis of somatic delusional disorder should replace the diagnosis of body dysmorphic disorder.

Paranoid personality disorder presents a diagnostic problem when the suspiciousness becomes so pronounced that it resembles a delusion. However, these disorders never become truly delusional and are distinguished in this way from delusional disorders.

8. Laboratory Examinations

Several laboratory examinations are useful in excluding other diseases that can present as a delusional disorder. Neuropsychological tests demonstrating cognitive dysfunction raise the possibility of a dementia or a psychotic disorder caused by 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.

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 (29) reviewed case reports that met DSM-IV criteria and reported treatment outcome. Because of the unsystematic nature of case reports, response rates should not be considered generalizable, but the findings do reflect recent treatment practices. Of 208 cases examined, 156 were of the somatic subtype, and 129 of these were treated with pimozide. The cumulative recovery rate was 71%. Only 4 of 27 patients treated with other antipsychotic agents recovered. The remaining subtypes comprised only 40 cases. Seven of the 14 patients treated with pimozide recovered, compared with 8 of 25 patients treated with other antipsychotic agents. Although pimozide has been 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 (30).

A few studies have outlined a particular cognitive style in delusional disorders (e.g., jumping too rapidly to conclusions (31) or a higher sensitivity to threat (32)). This has stimulated interest in using CBT to treat delusional disorder patients, and successful applications of such therapy having been recently reported (33).

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9
Anxiety Disorders

Richard C. Shelton, MD and Aaron J. Hunt, MD

Abstract Anxiety is a common and normal phenomenon, involving multiple brain regions, including the 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, including corticotrophin-releasing hormone, substance P, neuropeptide Y, cholecystokinin, and vasopressin. Anxiety is highly adaptive, and involves both acute fear that is related to an immediate threat, and anticipatory anxiety that is associated with a possible future threat. Certain individuals seem predisposed to develop anxiety disorders. Predisposing variables include genetic factors (that may function to 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, exclusively involves anticipatory fear (i.e., worry). Worries of everyday life are enhanced beyond any normal or adaptive functioning. Obsessive–compulsive disorder subsumes both obsessive ideation and compulsive behaviors. Obsessions are fears or worries that are fixated on unlikely events, and cannot be reduced by normal reassurance. Compulsions are repetitive behaviors that typically are in response to an obsession. For example, a person may have a fear of contamination that might lead to a terrible disease in themselves or someone else. This, then, leads to compulsive hand washing that may occur dozens of times per day. Although the person usually recognizes that the fear is excessive, they have difficulty controlling the worry. Finally, acute and posttraumatic stress disorders occur after a catastrophic, usually life-threatening event. People with these conditions experience persistent reexperiencing 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 Acute stress disorder · Antidepressants · Anxiety · Fear · Generalized anxiety disorder; Obsessive–compulsive disorder · Panic disorder · Posttraumatic stress disorder · Psychotherapy · Selective serotonin reuptake inhibitors · Social phobia; Specific phobia

1. Introduction

Anxiety disorders are common and often serious conditions that are associated with considerable morbidity. For example, rates of disability with certain anxiety disorders, such as panic disorder or posttraumatic stress disorder (PTSD) are high. In addition, 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 then 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 approximately 12% and the lifetime prevalence is nearly 20% (2). Specific and social phobias are the most common, with lifetime prevalence rates of

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6.7% and 12.1%, respectively. Moreover, anxiety disorders are commonly comorbid with other Axis I or II disorders, including major depression, dysthymia, personality disorders, substance abuse, or even other anxiety disorders.

1.1. The Neural Substrate of Anxiety

Anxiety, fear, aversion, and obsession 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 the locus ceruleus, and amygdala (Fig. 9.1). The amygdala 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 the 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 as well as inhibitory activity that is more direct. Hence, the frontal cortex and cingulate are significantly involved in the regulation of both emotional and behavioral response to fear-inducing stimuli.

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 system 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 nonthreatening 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 postsynaptic potential state. This inhibits subsequent action potentials until GABA is unbound and the chloride channels close, resulting in hyperpolarization. This decrease in neuronal firing seems to be related to the action of drugs that

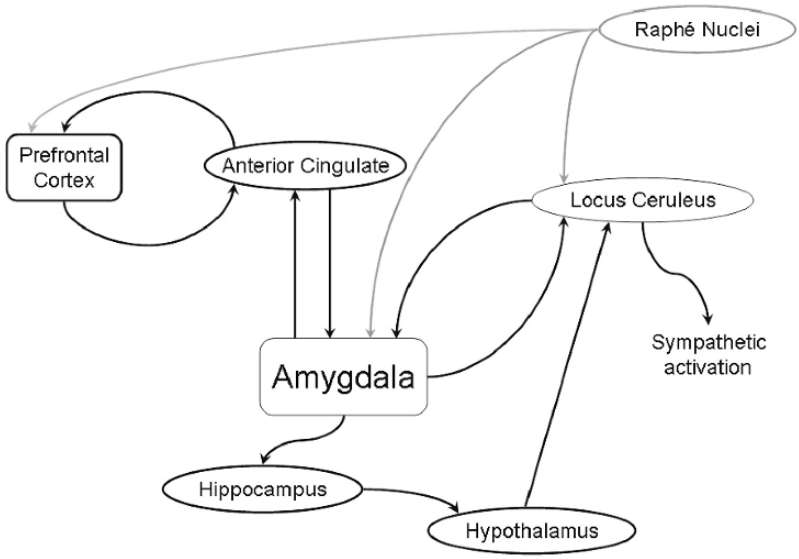

FIGURE 9.1. Neural substrates of anxiety. A simplified diagram of brain structures involved in the regulation of anxiety. Acute fear involves activation of both the locus ceruleus and amygdala; the amygdala also plays a key role in memory encoding related to fearful stimuli. The frontal cortex is involved 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 also serves a modulatory role. Serotonin, arising from the raphé nuclei, regulates activity in multiple brain areas.

act on GABA receptors; GABA activation inhibits anxiety and can induce sleep. There are direct-acting GABA agonists, such as baclofen and gabapentin, that exhibit antianxiety 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 central nervous system (CNS), with multiple receptor subtypes that can have opposing functions. However, the inhibition of amygdala activity seems 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 brainstem, is a significant mechanism mediating anxiety, and the locus ceruleus is thought to be an important brain structure in the generation of acute anxiety. Because 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 seems 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.

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 reexposure to similar threatening stimuli, behavioral responses are evoked 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 evoke an initial anxious response. There seems 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, seems to predispose to the subsequent development of certain anxiety disorders, such as social phobia (17). Constructed more broadly, the anxious or emotionally reactive temperament seems to predispose to a range of anxiety and depressive disorders. 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.

More than 20 years ago, a so-called tripartite model of mood and anxiety disorders was proposed (18–20). 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 anxiety (SA), representing physical symptoms related to acute fear. The NA axis tends to be elevated in all anxiety and mood disorders; that is, by definition, all of 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, whereas most anxiety disorders do not have the same problem (21, 22). One exception is social phobia, in which PA tends to be low. This may reflect the propensity of people with social phobia 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 some unique and many shared features to disorders of anxiety and mood. 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 SA 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 seem 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 (23). One common factor seems to be related to temperament, a tendency for heightened negative emotional responses to environmental stressors (termed neuroticism) (24). Temperament seems to have a significant genetic contribution, and the transmission of this trait is likely to increase the familial liability to this group of conditions.

TABLE 9.1. Criteria for panic attack (from DSM-IV-TR).

A discrete period of intense fear or discomfort, in which four (or more) of the following symptoms developed abruptly and reached a peak within 10 minutes:

1. Palpitations, pounding heart, or accelerated heart rate
2. Sweating
3. Trembling or shaking
4. Sensations of shortness of breath or smothering
5. Feeling of choking
6. Chest pain or discomfort
7. Nausea or abdominal distress
8. Feeling dizzy, unsteady, lightheaded, or faint
9. Derealization (feelings of unreality) or depersonalization (a sense of being detached from oneself)
10. Paresthesias (numbness or tingling sensations)
11. Chills or hot flushes
12. Fear of losing control or going crazy
13. Fear of dying

2. Panic Disorder

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 sudden unexpected 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.

2.2. Criteria and Diagnosis

The characteristic symptoms associated with a panic attack are listed in Table 9.1. A 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. 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 problem, 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 in section 2.3 below.

The DSM-IV criteria for diagnosing panic disorder are found in Table 9.2. Panic disorder is diagnosed after typical panic attacks followed by at least 1 month of one or more of the following:

TABLE 9.2. Diagnostic criteria for panic disorder without agoraphobia (from DSM-IV-TR).

A. Both (1) and (2):
   1. Recurrent unexpected panic attacks
   2. At least one of the attacks has been followed by 1 month (or more) of one (or more) of the following:
      (a) Persistent concern about having additional attacks
      (b) Worry about the implications of the attack or its consequences (e.g., losing control, having a heart attack, "going crazy")
      (c) A significant change in behavior related to the attacks
B. The panic attacks are not caused by the direct physiological effects of a substance or a general medical condition (e.g., hyperthyroidism)
C. The panic attacks are not better accounted for by another mental disorder, such as social phobia (e.g., occurring on exposure to feared social situations), specific phobia (e.g., on exposure to a specific phobic situation), OCD (e.g., on exposure to dirt in someone with an obsession about contamination), PTSD (e.g., in response to stimuli associated with a severe stressor), or separation anxiety disorder (e.g., in response to being away from home or close relatives)

- Persistent concerns about having more attacks: A panic attack is a traumatic experience, and people often develop worry about having more attacks. This is often associated with avoidance behavior.
- Worry about the implications of the attacks: 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.
- A significant change in behavior: If panic attacks continue to occur, most people will develop altered behavior patters, 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.

As with other psychiatric disorders, the diagnosis is excluded if the symptoms can be better accounted for by another psychiatric disorder (such as social phobia), a discreet 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–hypnotic drugs, benzodiazepines, or opiates.

2.3. Agoraphobia

DSM-IV agoraphobia is formally defined as a fear of being in circumstances from which escape is difficult or help is not available. Panic disorder is often accompanied by avoidance of situations with certain features. These may include places or circumstances: 1) in which a panic attack has occurred in the past; 2) from which escape would be difficult; 3) where help is not readily available; or 4) where the occurrence of the attack would be embarrassing. 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.

Unfortunately, the problem often builds over time and can become very pervasive. Some people may become completely unable to leave their homes. If untreated, panic attacks and avoidance behavior may result in progressive disability. Suicide can also occur, especially when panic is accompanied by depression, which occurs in approximately 40% of untreated patients.

Agoraphobia may also be diagnosed without panic disorder (Table 9.3), although this is uncommon. This usually occurs when there are relatively milder attacks or those with fewer then 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-IV. Very rarely, agoraphobic avoidance can develop without evidence of attacks at all; however, this is most commonly related to another mental disorder, such as social phobia, and would be diagnosed as such.

The relationship between panic attacks and agoraphobia often evolves in a predictable manner. Actually, mild or limited symptom attacks are not rare in the general population, and may never progress to panic disorder or agoraphobia. As experience with panic attacks builds, patients will tend to progressively expand the scope of avoidance behavior. Subsequently, this tends to make recovery more difficult.

2.4. Epidemiology

Recent epidemiological studies suggest that the 1-year prevalence rates of panic disorder are 2.1%, with a lifetime prevalence of 5% (25). Panic disorder with agoraphobia is more common than panic disorder without agoraphobia in both 1-year (0.6% versus 1.6%) and lifetime (1.1% versus 4%) prevalence rates. Certain factors tend to increase the risk for panic; these include female sex, 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 approximately ages 25 to 45 years.

TABLE 9.3. Diagnostic criteria for agoraphobia without history of panic disorder (from DSM-IV-TR).

A.	The presence of agoraphobia related to fear of developing panic-like symptoms (e.g., dizziness or diarrhea)
B.	Criteria have never been met for panic disorder
C.	The disturbance is not caused by the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition
D.	If an associated general medical condition is present, the fear described in Criterion A is clearly in excess of that usually associated with the condition

2.5. Etiology

2.5.1. Genetic and Biological Factors

Studies suggest that panic disorder is heritable, which contributes approximately 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 general population. The genetic diathesis is also supported by twin studies that have shown that monozygotic twins have a higher concordance rate than dizygotic twins (45% versus 15%) (26).

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).

Panic attacks themselves involve activation of cortical and subcortical regions, as well as increased sympathetic activity. 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 seems to occur via activation of locus ceruleus, the principal source of norepinephrine in the CNS. Norepinephrine increases cortical arousal, and stimulates the 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 numbness and tingling of limbs or lips, or dizziness. 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 (27). 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 potently 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 (28).

2.5.2. Psychological Factors

Patients with panic disorder showed markedly anxious responses to the bodily cues associated with panic attacks. Although anxious temperament or other cognitive predisposition may exist in people who develop panic, the exaggerated reactions to bodily sensations may be generated by 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 (29). This may account, in part, for the higher prevalence rate in women, because they are more likely to experience sexual abuse.

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 approximately 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, whereas 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 OCD 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, because the antianxiety 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 a stroke or myocardial infarction. Note, however, that the features of panic are very 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 myocardial infarction. On the other side of things, persons who have had a heart attack complain of characteristic myocardial infarction 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 myocardial infarction. 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 (ECG), exercise stress test, or magnetic resonance imaging (MRI) scan 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), whereas 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 SSRIs because patients may be more sensitive than average to the lower gastrointestinal side effects that commonly occur with these drugs.

A few medical conditions 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 tumor 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 very 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 very 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.

People with panic tend to be very 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 such as hyperthyroidism or hypothyroidism, angina, arrhythmias, or

vestibular disease significantly interfere 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 workup 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 primary care physician). 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 very severe.

2.7. Treatment

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 9.4 outlines common drugs with their daily dose ranges. Although many medications are used to treat anxiety, they tend to fall into two basic categories: antidepressants with antipanic properties and benzodiazepines.

2.7.1.1. Antidepressants

Of the medications that carry indications for the treatment of panic disorder, the selective SSRIs are the most commonly used. Although certain drugs, such as fluoxetine, paroxetine, and sertraline, have been granted an indication for panic disorder by the US Food and Drug Administration (FDA), the therapeutic benefit seems to be a class effect for drugs that block the uptake of serotonin. SSRIs are a 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 (MAOIs), are also very effective in reducing panic. However, their side effect and safety profile make them very 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.

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, such as desipramine. Furthermore, bupropion, which acts on presynaptic norepinephrine and dopamine, seems to be devoid of antipanic properties. In addition, buspirone, which has antianxiety properties for more 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 brain. Buspirone is a serotonin 1A partial agonist. Stimulation of these receptors actually increases the firing in the locus ceruleus, which is thought to underlie panic attacks.

Regardless of 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

TABLE 9.4. Medications with indications for panic disorder.

Medication	Starting dosage	Recommended daily dosage
SSRI		
• Paroxetine	10 mg qd	40–60 mg
• Fluoxetine	10 mg qd	20–60 mg
• Sertraline	25 mg qd	50–200 mg
SNRI/SSRI		
• Venlafaxine XR	37.5 mg qd	75–225 mg
Benzodiazepines		
• Alprazolam	0.5 mg tid	0.5–3 mg tid
• Alprazolam CR	0.5–1 mg qd	3–6 mg qd
• Clonazepam	0.25 mg bid	0.5–2 mg bid

Note that this table applies to regular dosing in healthy adults. Pediatric and elderly dosing will be different, and may not be indicated. Qd, once daily; tid, three time daily; bid, twice daily.

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- to 25-mg increments every 1 or 2 weeks until panic suppression is achieved. This may ultimately require standard antidepressant doses (e.g., 50 to 150 mg/day). However, it takes time to achieve the maximum effect dose. Similarly, starting at 10 to 25 mg of a tricyclic such as nortriptyline is appropriate, followed by increases in the same increments (i.e., 10–25 mg every 1 to 2 weeks) (30, 31).

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. Recently, 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) (32). 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 (33) This may occur more often with short half-life drugs, such as venlafaxine and paroxetine, although reactions with other drugs may occur. On the other hand, 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 (34, 35). Therefore, the decision may not be a simple one.

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 reduce initial anxiety, including 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 [CBT]) take effect.

Higher-potency benzodiazepines, such as alprazolam and clonazepam are very effective to suppress panic attacks, and both have carried an FDA indication for panic. The dosing range in clinical trials was 1 to 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/day. However, a more typical range for panic is 1 to 4 mg/day, divided. In both cases, the dose should be started low and titrated upward as needed. Beginning with 0.25 to 0.5 mg twice daily, the dose should be advanced within the dosing range in steps of 0.5 to 1.0 mg/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 overdosage.

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. 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 regarding 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.

2.7.2. Psychotherapy

A variety of therapies have been tested for panic, with varying success. Classic behavior therapy, which includes graded exposure (discussed in section 4.2.5 below), can be helpful. However, the best evidence base supports the use of CBT (36). Other kinds of therapy have limited usefulness in this condition.

CBT combines several components to manage the breadth of symptoms in panic disorder. For example, CBT incorporates classic behavioral therapy to deal with avoidance behavior. This involves graded reexposure to the feared place or thing. This may begin with relaxation with 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. However, 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 leads 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 (37, 38).

2.7.3. Course and Prognosis

The natural course of untreated disease is often chronic and outcomes can be poor. Many patients will see many professionals before arriving at an accurate diagnosis leading to effective treatment. This may be caused, in part, by 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.

3. Generalized Anxiety Disorder

3.1. Overview

An essential feature of GAD is unrealistic or excessive worry and apprehension regarding 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.

The symptoms of 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. Hence, the patient may never be free of worries—that is, negative anticipation of the "next bad thing." In addition, 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 memory difficulty. 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, diarrhea, and urinary frequency. GAD may also affect diet, with some people over eating and others restricting.

3.2. Diagnostic Criteria

The diagnostic criteria for GAD are found in Table 9.5. Excessive worry is the hallmark of this disorder. To diagnosis 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. Although these symptoms can coexist with other disorders, the anxiety experienced must be distinguished from other DSM-IV disorders. For instance, the patient's anxiety and ruminations cannot be about having a panic attack as in panic disorder, about social situations as in social phobia, or about 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.

3.3. Epidemiology

Epidemiological data suggest that the 1-year prevalence rate of GAD is roughly 2 to 5%, and lifetime prevalence rates have been estimated between 2 and 8% (39). Because 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 (40). 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 regarding 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.

TABLE 9.5. Diagnostic criteria for GAD (from DSM-IV-TR).

A. Excessive anxiety and worry occurring about multiple activities/events more days than not for at least 6 months
B. Difficulty controlling worry
C. Anxiety and worry associated with three or more of the following (with at least some symptoms present for more days than not for the past 6 months).
Note: only one item is required in children
1. Restlessness or feeling keyed up or on edge
2. Being easily fatigued
3. Difficulty concentrating or mind going blank
4. Irritability
5. Muscle tension
6. Sleep disturbance (difficulty falling or staying asleep, or restless unsatisfying sleep)

D. The focus of the anxiety and worry is not confined to features of an axis I disorder
E. The anxiety, worry, or physical symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning
F. The disturbance is not caused by the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition (e.g., hyperthyroidism) and does not occur exclusively during a mood disorder, a psychotic disorder, or a pervasive developmental disorder

Unfortunately, only approximately one quarter of patients are diagnosed.

3.4. Etiology

3.4.1. Genetics and Biological Factors

The propensity for GAD is at least is partially heritable, with strong influence of environmental factors (41). 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) (42). Temperament is partially heritable, and may serve as the foundation of risk for GAD (43). 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 (41, 44). 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 (21,22). Therefore, GAD has almost complete overlap with the symptoms of other mood and anxiety disorder. In fact, 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 (45). 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 propensity for 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 symptoms, and is regulated by serotonin and GABA, but also many other neurotransmitters. Therefore, dysregulation in any of several different modulators of the anxiety apparatus may result in persistent anxiety symptoms.

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 seems 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 adversive-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. Therefore, 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 that may increase the likelihood of the event actually occurring. An example would be a person who fears abandonment by a girl 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.

3.5. Treatment

3.5.1. Pharmacological

SSRIs or serotonin–norepinephrine reuptake inhibitors (SNRIs) are the most commonly prescribed psychotropics for the treatment of GAD. For both classes of drugs, standard antidepressants are commonly used. People with GAD, as a rule, are not as sensitive to side effects as are people 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 9.6.

Buspirone is a serotonin 1A receptor partial agonist, and has a moderate antianxiety effect. However, it is generally well tolerated. In particular, 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, are very potent antianxiety 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 CBT should be used before the regular use of benzodiazepines.

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 (46). Therefore, they should be avoided. Tricyclic antidepressants also are effective (47), but because of lack of tolerance and adverse side effects, they have given way to more well-tolerated agents, such as the SSRIs.

TABLE 9.6. Medications with indications for GAD.

Medication	Starting dosage	Recommended daily dosage
SSRIs		
• Paroxetine	10 mg qd	20–50 mg
• Escitalopram	10 mg qd	10–20 mg
Buspirone	7.5 mg bid	20–30 mg div bid/tid.
SSRI/SNRI		
• Venlafaxine XR	37.5 mg qd	75-225 mg

Note that this table applies to regular adult dosing. Pediatric and elderly dosing will be different, and may not be indicated. Qd, once daily; bid, twice daily; div, divided; tid, three time daily.

3.5.2. Psychological Treatment

Because of 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 that can be identified and addressed. 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, CBT has shown efficacy in treating generalized anxiety, and may be coupled with medication therapy (48). Techniques of cognitive therapy include cognitive restructuring; that is, improved reality testing appraisal of risk. This can be coupled with improving problem-solving skills and relaxation techniques. Other modes of therapies have limited empirical support.

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 GAD.

GAD may accompany most 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, and these features help distinguish the diagnosis. Similarly, elements that distinguish anxiety disorders include "true" obsessions and compulsions (OCD), panic attacks (panic disorder), circumscribed fears (specific and social phobia), and reexperiencing traumatic events (PTSD).

Certain physical illnesses share features with GAD, which can prove problematic if the physical illnesses are

not accurately excluded 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. An 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 associated anxiety symptoms; this would include stroke, Parkinsonism, Alzheimer's disease, 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 of many substances—such as caffeine, cocaine, amphetamine or other stimulants, hallucinogens, and marijuana, and typically resolve after discontinuation. Withdrawal from alcohol, benzodiazepines or other sedatives, and nicotine may be anxiogenic. Many other medications also contribute to the development of anxiety, including sympathomimetics, aminophylline, prescribed stimulants (amphetamines or methylphenidate), phenmetrazine, levodopa, antihistamines, albuterol (and related drugs), steroids, metoclopramide, 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 because of 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, interdose anxiety may be a particular problem with short half-life agents.

3.7. Course and Prognosis

GAD 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.

4. Phobic Disorders: Specific and Social Phobia

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 phobia 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.

4.2. Specific Phobia

With specific phobia, the stimulus may be an object or situation. Exposure to these things produces intense fear, anxiety, or feelings of aversion, leading one 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, similar to panic, anticipatory anxiety and avoidance of situations in which exposure to the phobic stimulus is possible, leading the person to modify their 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 their 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), who may completely avoid elevators. This may have an impact on their vocational choice or attainment.

4.2.1. Diagnostic Criteria

Diagnostic criteria for specific phobia are found in Table 9.7, along with a list of subtypes. Diagnostically, this disorder is differentiated from other anxiety disorders primarily because of a unique fear arising in very specific circumstances. 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 phobic patients (e.g., those with a blood phobia) have been noted to have a sharp fall in blood pressure, leading to dizziness and possible fainting.

4.2.2. Epidemiology

Specific phobia is one of the most common disorders, afflicting up to 25% of the population with mild symptoms. Phobias meeting full diagnostic criteria can be found in 8 to 10% of the population. Men and women are probably equally likely to experience phobias, but more women are more likely to present for treatment. Onset of symptoms may occur in childhood, and commonly before adult life. Little

TABLE 9.7. Diagnostic criteria for specific phobia (from DSM-IV-TR).

A. Marked and persistent fear that is excessive or unreasonable, cued by the presence or anticipation of a specific object or situation (e.g., flying, heights, animals, receiving an injection, seeing blood)
B. Exposure to the phobic stimulus almost invariably provokes an immediate anxiety response, which may take the form of a situationally bound or situationally predisposed panic attack. **Note:** In children, the anxiety may be expressed by crying, tantrums, freezing, or clinging
C. The person recognizes that the fear is excessive or unreasonable. **Note:** In children, this feature may be absent
D. The phobic situation(s) is avoided or else is endured with intense anxiety or distress
E. The avoidance, anxious anticipation, or distress in the feared situation(s) interferes significantly with the person's normal routine, occupational (or academic) functioning, or social activities or relationships, or there is marked distress about having the phobia
F. In individuals younger than age 18 years, the duration is at least 6 months
G. The anxiety, panic attacks, or phobic avoidance associated with the specific object or situation are not better accounted for by another mental disorder, such as OCD (e.g., fear of dirt in someone with an obsession about contamination), PTSD (e.g., avoidance of stimuli associated with a severe stressor), separation anxiety disorder (e.g., avoidance of school), social phobia (e.g., avoidance of social situations because of fear of embarrassment), panic disorder with agoraphobia, or agoraphobia without history of panic disorder

Subtypes:
Animal type
Natural environment type (e.g., heights, storms, water)
Blood-injection-injury type
Situational type (e.g., airplanes, elevators, enclosed places)
Other type (e.g., fear of choking, vomiting, or contracting an illness; in children, fear of loud sounds or costumed characters)

is known regarding the course of untreated specific phobias, because phobias may resolve spontaneously or people learn to cope with these stressors, and, thus, they may never come to attention.

4.2.3. Etiology

Little is known regarding 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 more prevalently than in the general population, and there may be a predisposition to a phobia of the same type. In addition, people with other anxiety disorders, such as panic or social phobia, may be at increased risk. What generally is not true is that phobias 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 Sect. 6). However, previous abuse or similar early traumas do not seem to predispose to phobias.

Specific phobia involves panic-like responses, and is thought to involve the same pathways as panic disorder (see Sect. 2). 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 are the amygdala and hippocampus. However, ultimately, midbrain structures, particularly the locus ceruleus, are likely to be involved.

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. In addition, social phobia may result in fear and avoidance of certain circumstances that involve exposure to scrutiny by others, as described in section 4.3 below. With 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 helps differentiate between these two disorders. In fact, specific phobia is very 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.

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 simple 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.

4.2.6. Course and Prognosis

Phobias can develop throughout the lifespan. 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 with lack of motivation or participation in therapy.

4.3. Social Phobia

4.3.1. Overview and Presentation

Social phobia (also referred to as social anxiety disorder) is defined as excessive fear of situations in which a person might be negatively evaluated by others or might do something embarrassing. This fear may be coupled with a fear of being unable to avoid or escape situations. In social situations, people may experience anxiety that approaches that experienced in a panic attack. Consequently, the situations are 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 phobia, 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 phobia. 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 phobias usually have 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 phobia 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.

4.3.2. Diagnostic Criteria

Diagnostic criteria are found in Table 9.8. In social phobia, 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 one may endure 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. To meet full diagnostic criteria, a specific time frame is not specified for adults, although long durations for the illness are the norm. However, children must have a 6-month minimum presence of symptomology before meeting criteria. As in all disorders, social phobia must be distinguished from general medical conditions, the effects of substances, or other mental disorders. For

TABLE 9.8. Diagnostic criteria for social phobia (from DSM-IV-TR).

A. A marked and persistent fear of one or more social or performance situations in which the person is exposed to unfamiliar people or to possible scrutiny by others. The individual fears that they will act in a way (or show anxiety symptoms) that will be humiliating or embarrassing. **Note:** In children, there must be evidence of the capacity for age-appropriate social relationships with familiar people and the anxiety must occur in peer settings, not just in interactions with adults
B. Exposure to the feared social situation almost invariably provokes anxiety, which may take the form of a situationally bound or situationally predisposed panic attack. **Note:** In children, the anxiety may be expressed by crying, tantrums, freezing, or shrinking from social situations with unfamiliar people
C. The person recognizes that the fear is excessive or unreasonable. **Note:** In children, this feature may be absent
D. The feared social or performance situations are avoided or else are endured with intense anxiety or distress
E. The avoidance, anxious anticipation, or distress in the feared social or performance situation(s) interferes significantly with the person's normal routine, occupational (academic) functioning, or social activities or relationships, or there is marked distress about having the phobia
F. In individuals younger than age 18 years, the duration is at least 6 months
G. The fear or avoidance is not caused by the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition and is not better accounted for by another mental disorder (e.g., panic disorder with or without agoraphobia, separation anxiety disorder, BDD, a pervasive developmental disorder, or schizoid personality disorder)
H. If a general medical condition or another mental disorder is present, the fear in Criterion A is unrelated to it, e.g., the fear is not of stuttering, trembling in Parkinson's disease, or exhibiting abnormal eating behavior in anorexia nervosa or bulimia nervosa

Specify whether:
Generalized: if the fears include most social situations (also consider the additional diagnosis of avoidant personality disorder)

example, fears of social situations are a consequence of panic disorder.

4.3.3. Epidemiology

The 6-month prevalence of social phobia is almost 3%, with a lifetime prevalence rate of 5% (2). However, this may represent an underestimation, because mild symptoms are common. 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. Women have a greater prevalence rate than men in the population, but an equal portion seem to present for treatment. The age of onset is usually during adolescence.

4.3.4. Etiology

Genetics and biology may play a significant role in the development of this disorder. Family and twin studies suggest that genetics contributes a moderate level of risk, and that the remainder of the risk is largely caused by environmentally specific factors. As noted for other anxiety disorders, the emotionally reactive temperament seems to contribute significantly to the predisposition to phobias in general (24). Best-fit models support the notion that genetics, familial (i.e., "shared") environment, and individual-specific environmental factors contribute independent, but interacting, risk (49, 50).

There is also evidence to support that temperament and other factors, such as cognitive distortions, play a role in the development of social phobia, along with interaction with the environment. Children who have a first-degree relative with social phobia seem to be at a twofold to threefold greater risk for developing social phobia 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.

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, nonthreatening 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, a phenomenon that, almost by definition, does not occur with phobic disorders. Therefore, although phobias may, on the surface, seem to correspond to a classic conditioning model, certain features are not consistent with this view. Therefore, sustained phobias are likely to arise from a mixed model that may or may not depend on the presentation of an environmental threat.

4.3.5. Differential Diagnosis and Comorbidity

The diagnosis of social phobia requires differentiation from other similar-appearing clinical pictures. The most significant differential is with other anxiety disorders. As noted, interviewing to elicit specific features is most helpful. Thus, although people with OCD 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 phobia 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 PTSD 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. For example, Cluster A personality disorders such as schizoid or schizotypal may have little social interaction. However, this is not the result of social anxiety per se, and is preferred by the individual. Stated simply, they may not desire social interaction. 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, is that generalized social phobia is difficult to distinguish from avoidant personality and, in fact, may be the same condition.

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 involves 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).

4.3.6. Treatment

Both pharmacological and psychotherapeutic methods are useful in the treatment of social phobia. A number of drugs

carry specific indications for its treatment. In particular, these include the SSRIs paroxetine and sertraline as well as the extended-release version of the SNRI venlafaxine. A summary of these medications along with their common dosages are found in Table 9.9. The doses used are similar to those used for major depression. The problem of increased anxiety early in treatment with SSRIs and SNRIs seen in panic disorder is not as prominent with social phobia. 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 used 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 before 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 before being implemented. Note that many people have anxiety in multiple social situations, or may have unpredictable social interactions, making the use of benzodiazepines problematic. Because of 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 phobia (51). Older drugs, such as the MAOI, 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 before the social interaction because of the potential for side effects.

Traditional behavioral and CBT are effective therapies. 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 to the therapist, to a small number of family and friends, to a larger number of familiar people, and, eventually, working up to large groups of unfamiliar people.

TABLE 9.9. Medications with indications for social anxiety disorder.

Medication	Starting dosage	Recommended daily dosage
SSRIs		
• Paroxetine	10 mg qd	20–50 mg
• Paroxetine CR	12.5 mg	12.5–37.5 mg
• Sertraline	25 mg qd	50–200 mg
SSRI/SNRI		
• Venlafaxine XR	37.5–75 mg qd	75–225 mg

Note that this table applies to regular adult dosing. Pediatric and elderly dosing will be different, and may not be indicated. Qd, once daily.

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 to 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 very effective in producing long-term improvement. In addition, the use of medications in the absence of behavioral methods is often only partially effective.

4.3.7. Course and Prognosis

The course of social phobia 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.

5. Obsessive–Compulsive Disorder

5.1. Overview and Presentation

OCD is an anxiety disorder in which a person experiences uncontrolled and intrusive thoughts (obsessions) and repetitive or ritualistic behaviors (compulsions). Most patients experience both obsessions and compulsions. Common obsessions include fears about contamination; pathological doubt about things like turning off a stove, locking doors, or the like; a need for symmetry; and fears about loss of control of sexual or aggressive drives. Obsessions are most often paired with corresponding compulsive behaviors. For example, fears about contamination typically result in washing behavior (e.g., hands), pathological doubt results in repeated checking (of doors, windows, stove, etc.), a need for symmetry results in straightening or counting, and so forth. To meet full diagnostic criteria, the obsessions and compulsions must be time consuming (an hour or more per day) or cause significant impairment or distress. Some patients will experience multiple obsessions and compulsions; however, a single obsessive–compulsive pair will typically predominate.

Obsessions may come out of the blue or may be stimulated by something in the environment. For example, if someone with OCD uses a public restroom, they may need to wash their hands repeatedly. People with a contamination obsession may wash their hands 50 or more times per day. Contamination fears may become more generalized, requiring a person to repeatedly wash hands, body, clothing, or objects in the environment. They may also engage in avoidance behavior, such as keeping away from restrooms. Because many objects or situations may stimulate the obsessions and compulsions, their life may become very restricted.

Obsessions may seem simple on the surface: my hands feel contaminated, I wash them. However, they often are much more complex. For example, the fear of contamination may not just be about becoming ill. Typically, it is about picking up some deadly disease (e.g., HIV) and transmitting it to others. Similarly, checking is often about the safety of others. For example, the person may have images of the stove being left on, catching the house on fire injuring or killing family members, and then the fire spreading to surrounding houses.

Functional impairment typically occurs as the result of the time required to engage in the necessary behaviors to reduce anxiety. They may spend many hours engaging in these behaviors and this can be significantly debilitating. The feelings of anxiety or aversion will abate after the performance of a compulsive behavior. However, the feelings will build again, especially after the exposure to an environmental stimulus (although an external stimulus is not required). Patients often feel this as a sense of growing tension, which is discharged with the compulsion. If the behavior is avoided, often they have a sense of anxiety, aversion, and incompleteness. Some will even experience panic-like reactions on exposure if they cannot engage in the compulsion.

5.2. Diagnostic Criteria

Diagnostic criteria are found in Table 9.10. Although the features may superficially seem to be like other conditions, there are important differences. For example, although the obsession (for example, contamination fears) may seem illogical or even delusional, almost all patients recognize that the obsessive thoughts and compulsive behaviors are excessive. As a result, they often see the thoughts and behaviors as being nonsensical, and are embarrassed to discuss them openly. Rarely, people can lack insight into the nature of their obsessions and compulsions. This may be particularly true with children with OCD. However, if this is the case, an alternative diagnosis of a psychotic disorder should be entertained.

By DSM-IV-TR criteria, obsessions must be recurrent, intrusive, and cause anxiety when present. They are not simply excessive worries about everyday life, and the person will usually perform behaviors to stop them. Compulsions are behaviors that in most cases are intended to counteract the distress caused by associated obsessions. Compulsions may be physical or mental acts that are often performed in a very rigid, ritualistic fashion.

Rituals that are more complex may emerge. For example, people may have to compulsively repeat certain words or phrases. They may have to engage in complex counting or mathematical exercises. Alternatively, complicated rituals with regard to grooming (such as hair combing) or the preparation of food may occur. Rituals may be less clearly linked to specific obsessions. However, the same pattern still emerges: the person feels compelled to perform rituals to reduce or prevent feelings of anxiety, dread, or tension. Patients may incorporate these behaviors into their everyday life, but usually recognize that they are abnormal.

5.3. Epidemiology

The general prevalence of OCD is approximately 2 to 3% (25). However, the majority of patients do not come to attention because of embarrassment associated with their symptoms.

Table 9.10. Diagnostic criteria for OCD.

A. Either obsessions or compulsions:

Obsessions as defined by (1), (2), (3), and (4):

1. Recurrent and persistent thoughts, impulses, or images that are experienced, at some time during the disturbance, as intrusive and inappropriate and that cause marked anxiety or distress
2. The thoughts, impulses, or images are not simply excessive worries about real-life problems
3. The person attempts to ignore or suppress such thoughts, impulses, or images, or to neutralize them with some other thought or action
4. The person recognizes that the obsessional thoughts, impulses, or images are a product of their own mind (not imposed from without as in thought insertion)

Compulsions as defined by (1) and (2):

1. Repetitive behaviors (e.g., hand washing, ordering, checking) or mental acts (e.g., praying, counting, repeating words silently) that the person feels driven to perform in response to an obsession, or according to rules that must be applied rigidly
2. The behaviors or mental acts are aimed at preventing or reducing distress or preventing some dreaded event or situation; however, these behaviors or mental acts either are not connected in a realistic way with what they are designed to neutralize or prevent or are clearly excessive

B. At some point during the course of the disorder, the person has recognized that the obsessions or compulsions are excessive or unreasonable. **Note:** This does not apply to children

C. The obsessions or compulsions cause marked distress, are time consuming (take more than 1 hour a day), or significantly interfere with the person's normal routine, occupational (or academic) functioning, or usual social activities or relationships

D. If another Axis I disorder is present, the content of the obsessions or compulsions is not restricted to it (e.g., preoccupation with food in the presence of an eating disorder; hair pulling in the presence of trichotillomania; concern with appearance in the presence of BDD; preoccupation with drugs in the presence of a substance use disorder; preoccupation with having a serious illness in the presence of hypochondriasis; preoccupation with sexual urges or fantasies in the presence of a paraphilia; or guilty ruminations in the presence of major depressive disorder)

E. The disturbance is not caused by the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition

Specify whether :

With poor insight: if, for most of the time during the current episode, the person does not recognize that the obsessions and compulsions are excessive or unreasonable

However, they may present with dermatitis of the hands from washing or complaints (from the patient or significant other) about an inability to complete tasks. Onset typically occurs in the 20s or early 30s. Occasionally, however, OCD can be seen in children. In fact, the related condition, trichotillomania (compulsive hair pulling) is a common cause of hair loss in children (52–54). Men and women seem equally affected.

5.4. Etiology

OCD seems to be genetic, and heritability accounts for approximately 50% of the incidence variance, and unique environmental influences account for most of the remainder (55). There seems to be a genetic basis for OCD; for example, monozygotic twins tend to show a relatively high concordance rate. In addition, OCD seems to share genetic liability with a range of other mental and neurological conditions, such as tic disorders.

OCD has been hypothesized to involve orbitofrontal, cingulate, and striatal regions, what has been called a "cortico–basal ganglia network" or "obsessive–compulsive circuit" (56). This is a neural system that is known to be involved in the learning of repetitive (i.e., "habit") behaviors (56). The involvement of a circuit containing orbitofrontal and cingulate cortex and striatum (specifically the caudate nucleus) raises issues regarding the regulation of movement, habit behavior, and emotion.

Understanding this interplay requires an appreciation of the relationship between OCD and tic disorders. OCD is common among people with Gilles de la Tourette syndrome, a complex condition involving multifocal tics and involuntary vocalizations, throat clearing, grunting, or even cursing (57). Tourette's syndrome and OCD share multiple features. Most particularly, people with Tourette's syndrome experience a premonitory urge before the occurrence of tics or other behavior. Similar to OCD, this often includes a progressive feeling of distress or tension that is discharged by the action. Moreover, people are able to suppress the action for a period; however, the feelings will build in intensity until discharged by the act. In addition, a sizeable number of people with Tourette's syndrome have otherwise typical OCD. Tourette's syndrome seems to involve the same orbitofrontal–striatal circuits as hypothesized for OCD (57, 58).

OCD may occur after childhood streptococcal infections. This condition is known as "pediatric autoimmune neuropsychiatric disorder associated with streptococcal infections" (PANDAS) (59). This condition occurs after group-A beta-hemolytic streptococcus infections, and subsequent exacerbations may occur after re-infection. Generally, five criteria are needed to make the diagnosis: the presence of OCD or tic disorder, prepubertal age of onset, abrupt onset with a relapsing and remitting course, association with neurological abnormalities (e.g., tics or motor hyperactivity), and a temporal association between these features and a group-A beta-hemolytic streptococcus infection (59). This condition is very similar to Sydenham's chorea, which can occur in adults. It is thought to be mediated by an autoimmune response directed toward the basal ganglia as a result of cross-reactivity of antibodies to the group-A beta-hemolytic streptococcus. As with rheumatic fever, prompt antibiotic treatment may prevent PANDAS.

A number of neurotransmitter systems have been postulated to be involved, most particularly serotonin (60–62). The rationale implicating serotonin is based in part on the effectiveness of drugs that act on serotonin in reducing obsessions and compulsions, and the effects of serotonin agonist agents on the symptoms. Note, however, that the logic of the connection to treatment response is based on circular reasoning—i.e., "OCD improves with drugs that act on the serotonin system, therefore, serotonin is involved in the pathophysiology of OCD." As noted earlier, the effects of SSRIs may not be specific to the condition, and may occur via the suppression of symptoms such as anxiety, which, secondarily, will reduce obsessions and compulsions. Serotonin agonist drugs such as metachlorophenylpiperazine (mCPP), a nonspecific agonist at serotonin 2 receptors, can dramatically exacerbate the symptoms of OCD. However, mCPP nonspecifically increases anxiety and, thereby, may increase OCD symptoms.

Alternatively, dopamine and the interactions of the dopamine and serotonin systems in the genesis of OCD have been postulated (62). Dopamine seems to be involved in tic disorders including Tourette's syndrome. Dopamine agonist increase and dopamine 2 (D2) receptor antagonists decrease tics, although D2 antagonists alone do not improve OCD. Moreover, the endocrinological (e.g., prolactin) responses to both serotonin and dopamine agonists are abnormal in OCD (60). Although suggestive, the connections between these transmitters and OCD remain obscure.

5.5. Differential Diagnosis and Comorbidity

Many other psychiatric disorders can have obsessive or even compulsive features. Major depression often involves negative rumination, however, the content is typically different. People with OCD have fears that are peculiar, and usually recognize them as such. People with other anxiety disorders also have ruminative thoughts, and care must be taken in distinguishing the features. For example, people with GAD may worry about catastrophic things; however, this is found among other worries, which all reflect exaggerations of normal life concerns. People with panic, phobic disorders, or PTSD may also worry. However, there the content is specific to that condition—e.g., in panic disorder, the fear is about the occurrence of a panic attack; with phobias, the fear is about exposure to the stimulus. Eating disorders such as anorexia nervosa and bulimia may involve pathological rumination about diet and weight, and even ritual-like behaviors toward eating. However, the thoughts are restricted to eating and weight gain. Finally, with these other conditions, the thoughts do not lead to compulsive behavior. Therefore, OCD is diagnosable when

the obsessional features are not better accounted for by other disorders.

People with schizophrenia or other psychotic disorders may have both obsessive thoughts and compulsion-like behaviors. The thought content will have certain distinguishing features, such as bizarreness, fears of persecution, or even delusions about sickness or disaster. By definition, the psychotic person does not recognize the implausibility of the concerns, unlike the person with OCD. Abnormal motor behaviors often occur as well. For example, stereotypy involves voluntary repetitive behaviors or speech, but these occur in the absence of specific obsessive thoughts and they are not intended to reduce tension or distress. In addition, the behaviors or speech are not purposeful and can involve things such as mechanically moving the arm up and down or repeating a word incessantly. Alternatively, OCD does not involve disorganization of thought or delusions.

There is a range of other psychiatric disorders that share features with OCD, and are sometimes included in a spectrum of OCD-like conditions. These would include disorders of impulse control, such as kleptomania and pathological gambling, or paraphilias. In these conditions, thoughts are fixed on the object of the impulse, and people engage in compulsive-like repetitions of complex behavior, such as stealing. The distinction from OCD is relatively clear when the target of the obsession is identified. However, people affected with these conditions describe a similar buildup of distress or tension that is discharged with the performance of the act.

Somatoform disorders, such as hypochondriasis and body dysmorphic disorder (BDD), involve intensely obsessive thinking, with a fixation on body health or appearance. BDD is characterized with preoccupation with physical appearance; in this condition, people have a obsessive fixation on the appearance of a body part, such as the nose or ears. They may compulsively obtain plastic surgeries to "fix" the appearance. However, they do not see the behavior as abnormal or excessive.

Neurological disorders may present with frank obsessive and compulsive symptoms. As already noted, Tourette's syndrome and other tic disorders often present with OCD. Moreover, OCD may occur after an insult to the brain, such as trauma, encephalitis, multiple sclerosis, or brain tumors. Further, stimulant drugs, such as cocaine, used over an extended period, may lead to the development of obsessional thinking and compulsive behavior, although this resolves with the removal of the drug.

Certain personality disorders, particularly obsessive–compulsive personality disorder (OCPD), may be confused with OCD. With OCPD, the very diagnostic terminology may generate this confusion. In OCPD, people are preoccupied with order in their lives. They tend to focus on details, organization, rules, and order, and will often keep lists. They can be highly perfectionistic, and have excessively high standards of performance for themselves and others. They can be very scrupulous regarding morality and ethics, work, and money. However, they do not have typical obsessions or compulsions, and most often do not see their behavior as pathological.

5.6. Treatment

The SSRIs, such as fluoxetine, sertraline, fluvoxamine, and paroxetine, and the potent serotonin reuptake inhibitor, clomipramine, are most commonly used for OCD. Agents that carry an FDA indication for OCD are found in Table 9.11. Serotonin uptake inhibitors usually reduce the intensity of the symptoms, but are not curative. Many patients will have residual symptoms even after treatment with higher doses of these drugs. This situation may be improved with the addition of behavior therapies.

As a group, persons with OCD are not as fearful as people with other anxiety disorders, such as panic disorder. Therefore, their treatment with SSRIs can start at standard antidepressant doses. For example, paroxetine would be initiated at 20 mg/day, as with depression. The dose should be advanced as needed and tolerated through the typical therapeutic range. Some have advocated using higher doses in OCD than in depression, although the empirical support for this is lacking. Of note, however, is that the response to SSRIs may be slow and may take several weeks to reach maximum response.

Behavioral therapies are a mainstay of treatment for the condition, particularly because medications are usually not fully effective if administered alone. Behavioral treatment typically involves exposure with response prevention (63). People are exposed to stimuli that generate obsessions and compulsions, gradually increasing the amount of time spent in

TABLE 9.11. Medications with indications for OCD.

Medication	Starting dosage	Recommended daily dosage
SSRIs		
• Fluoxetine	20 mg qd	20–80 mg
• Paroxetine	20 mg qd	40 mg
• Sertraline	50 mg qd	50–200 mg
• Fluvoxamine	50 mg qhs	50–150 mg bid
TCA		
• Clomipramine	25 mg qhs	50–150 mg qhs

Note that table applies to regular adult dosing. Pediatric and elderly dosing will be different, and may not be indicated. Qd, once daily; qhs, every hour of sleep; bid, twice daily.

proximity. This is coupled with response prevention; that is, they are prevented from escaping or engaging in the associated compulsive behaviors. Some patients may be able to complete the tasks on their own, whereas others may need a therapist or facilitator present to do exposure. Often the overt compulsions become extinguished rapidly; however, premature discontinuation of treatment often results in a quick relapse. The anxiety, tension, and compulsive behaviors gradually dissipate, and many patients become largely symptom free. Alternatively, some people may need to engage in the exposure with response prevention occasionally thereafter to maintain the effect, although this may be done on their own (64). Adaptations of CBT may also be used. However, note that this is usually done with standard exposure therapy, and the necessity of the cognitive component has been questioned (65).

5.7. Course and Prognosis

OCD is usually a chronic disorder with a waxing and waning across a person's life. If left untreated, OCD may cause significant functional impairment. Alternatively, with treatment, symptoms will abate, although mild residual symptoms may continue. In addition, relapses may occur, requiring new intervention. Serotoninergic drugs such as the SSRIs are effective as long as they continue, but if they are discontinued, relapse is common. Unfortunately, many people do not have adequate access to treatments. This may be the result of finances, including lack of insurance, and the possible lack of available treatment, particularly behavior therapy. Unfortunately, OCD is often not recognized, and misdiagnosis is common. Even if diagnosed, OCD may have taken years to be recognized, during which time, functional impairment can accumulate. Therefore, early diagnosis and treatment is essential.

6. Trauma-Related Disorders: PTSD and Acute Stress Disorder

6.1. Overview and Presentation

Acute stress disorder (ASD) and 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. The majority of people do not experience lasting effects of exposure to severe threats; many develop ASD, only to recover completely. In the case of PTSD, symptoms may manifest immediately or after months or even years after an event happens.

ASD 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 ASD. However, ASD and PTSD have many common elements.

6.2. Diagnosis

Criteria for ASD are found in Table 9.12 and criteria for PTSD are found in Table 9.13. ASD and PTSD share many common characteristics, but have some key distinguishing features. Both of them require exposure to a traumatic event, most often that involves a threat to their life or others. They have similar symptomology; the temporal onset and duration of symptoms distinguish them. ASD requires a minimum of 2 days from the 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 intermediary disorder on a continuum of immediate reactions to stressors and PTSD, which has to be present for at least 1 month. If symptoms last longer than 6 months, then PTSD is considered chronic in nature.

A formal diagnosis of ASD or PTSD requires that a person experience at least one extremely traumatic event, that is, life-threatening situations, 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 after the event that may be severe.

Diagnosing these disorders requires three concurrent ongoing sets of symptoms. First, the person must exhibit so-called reexperiencing; that is, the person will experience reliving of events and feeling 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. Secondly, the flood of intense feelings and experiences can be overwhelming for a person, and drive physiological arousal and activation. Lastly, these experiences will result in avoidance of triggers for the anxiety—that is, reminders of the event. For example, combat survivors often avoid movies of the same type.

6.3. Epidemiology

The epidemiology of PTSD and ASD is directly associated with exposure to trauma. It is estimated that 20 to 30% of those who are exposed to a truly life-threatening situation will experience persistent symptoms. The lifetime prevalence of PTSD in the general population is approximately 8%, although rates are higher among women, children, and the elderly (66). Many people who have been exposed to traumatic events may not meet full criteria for ASD or PTSD, but may have significant symptoms; according to DSM-IV,

TABLE 9.12. Diagnostic criteria for ASD (from DSM-IV-TR).

A. The person has been exposed to a traumatic event in which both of the following were present:
   1. The person experienced, witnessed, or was confronted with an event or events that involved actual or threatened death or serious injury, or a threat to the physical integrity of self or others
   2. The person's response involved intense fear, helplessness, or horror
B. Either while experiencing or after experiencing the distressing event, the individual has three (or more) of the following dissociative symptoms:
   1. A subjective sense of numbing, detachment, or absence of emotional responsiveness
   2. A reduction in awareness of his or her surroundings (e.g., "being in a daze")
   3. Derealization
   4. Depersonalization
   5. Dissociative amnesia (i.e., inability to recall an important aspect of the trauma)
C. The traumatic event is persistently reexperienced in at least one of the following ways: recurrent images, thoughts, dreams, illusions, flashback episodes, or a sense of reliving the experience; or distress on exposure to reminders of the traumatic event
D. Marked avoidance of stimuli that arouse recollections of the trauma (e.g., thoughts, feelings, conversations, activities, places, people)
E. Marked symptoms of anxiety or increased arousal (e.g., difficulty sleeping, irritability, poor concentration, hypervigilance, exaggerated startle response, motor restlessness)
F. The disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning or impairs the individual's ability to pursue some necessary task, such as obtaining necessary assistance or mobilizing personal resources by telling family members about the traumatic experience
G. The disturbance lasts for a minimum of 2 days and a maximum of 4 weeks and occurs within 4 weeks of the traumatic event
H. The disturbance is not caused by the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition, is not better accounted for by brief psychotic disorder, and is not merely an exacerbation of a preexisting Axis I or Axis II disorder

TABLE 9.13. Diagnostic criteria for PTSD (from DSM-IV-TR).

A. The person has been exposed to a traumatic event in which both of the following were present:
   1. The person experienced, witnessed, or was confronted with an event or events that involved actual or threatened death or serious injury, or a threat to the physical integrity of self or others
   2. The person's response involved intense fear, helplessness, or horror. **Note:** In children, this may be expressed instead by disorganized or agitated behavior
B. The traumatic event is persistently reexperienced in one (or more) of the following ways:
   1. Recurrent and intrusive distressing recollections of the event, including images, thoughts, or perceptions. **Note:** In young children, repetitive play may occur in which themes or aspects of the trauma are expressed
   2. Recurrent distressing dreams of the event. **Note:** In children, there may be frightening dreams without recognizable content
   3. Acting or feeling as if the traumatic event were recurring (includes a sense of reliving the experience, illusions, hallucinations, and dissociative flashback episodes, including those that occur on awakening or when intoxicated). **Note:** In young children, trauma-specific reenactment may occur
   4. Intense psychological distress at exposure to internal or external cues that symbolize or resemble an aspect of the traumatic event
   5. Physiological reactivity on exposure to internal or external cues that symbolize or resemble an aspect of the traumatic event
C. Persistent avoidance of stimuli associated with the trauma and numbing of general responsiveness (not present before the trauma), as indicated by three (or more) of the following:
   1. Efforts to avoid thoughts, feelings, or conversations associated with the trauma
   2. Efforts to avoid activities, places, or people that arouse recollections of the trauma
   3. Inability to recall an important aspect of the trauma
   4. Markedly diminished interest or participation in significant activities
   5. Feeling of detachment or estrangement from others
   6. Restricted range of affect (e.g., unable to have loving feelings)
   7. Sense of a foreshortened future (e.g., does not expect to have a career, marriage, children, or a normal life span)
D. Persistent symptoms of increased arousal (not present before the trauma), as indicated by two (or more) of the following:
   1. Difficulty falling or staying asleep
   2. Irritability or outbursts of anger
   3. Difficulty concentrating
   4. Hypervigilance
   5. Exaggerated startle response
E. Duration of the disturbance (symptoms in Criteria B, C, and D) is more than 1 month
F. The disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning

Specify whether:
   Acute: if duration of symptoms is less than 3 months
   Chronic: if duration of symptoms is 3 months or more

Specify whether:
   With delayed onset: if onset of symptoms is at least 6 months after the stressor

this may be diagnosed as an anxiety disorder not otherwise specified. 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, or those exposed to serious natural disasters, such as earthquakes, are at risk.

6.4. 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, because only a 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 seems to be familial, and not caused entirely by shared environmental factors such as abuse (67). Clearly, even with a genetic predisposition, the occurrence of ASD or PTSD requires traumas that are specific to an individual (67). Shared and nonshared environmental factors may be difficult to tease apart; for example, siblings may all experience abuse, although 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.

The vulnerability to PTSD may have to do with genetic factors involving the stress axis. Altered regulation of the hypothalamic -pituitary -adrenal (HPA) axis is evident in PTSD. Unlike that seen in some patients with depression, the HPA axis abnormality involves cortisol levels below normal and an enhanced feedback inhibition by cortisol (or analogs such as dexamethasone) (68). The opposite pattern is seen in depression without co-morbid PTSD; that is, persistently elevated cortisol and blunted feedback suppression of the HPA axis. Therefore, PTSD appears to be associated with a reduced responsiveness of the HPA axis.

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 (69–71). However, the causal relationship is not clear.

Imaging studies suggest the involvement of specific brain regions in PTSD, in particularly, the hippocampus, amygdala, and frontal cortex (72). Functional MRI (fMRI) studies of exposure to reminders of the trauma suggest that the amygdala is hyperreactive. Further, the hippocampus often is reduced in volume (72), a phenomenon that may be associated with altered regulation of cortisol (73). Altered higher brain regulation of stress reactivity may be a consequence of trauma (72).

6.5. 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 after 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-IV Axis I disorders, such as major depression. However, because the treatment is very 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, because 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 regarding 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?; and 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 fabricated, but the patient may or may not be aware of the fabrication. However, they are not aware of the connection between the story and the secondary gain it is intended to

achieve. For example, a person may be able to avoid a major life responsibility, such as work, via fabricated claims. In addition, they may achieve attention, nurturance, and other desirable outcomes. This may be difficult to distinguish from actual PTSD, because it may occur after a major trauma, and can co-occur with other symptoms or syndromes, such as depression or personality disorder. With malingering, the secondary gain is conscious and the fabrication intentional. Therefore, exaggerated claims of injury (in this case PTSD) may occur as a result of a desire for compensation, to avoid prosecution for a crime, or to avoid work or other responsibilities.

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, and alcohol or drug withdrawal.

6.6. 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 an extended social support network, such as family members, if 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 9.14, although 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 antianxiety drugs such as benzodiazepines. However, if the acute response is severe, or if more serious depression is comorbid, then an antidepressant is indicated.

TABLE 9.14. Medications with indications for PTSD.

Medication	Starting dosage	Recommended daily dosage
SSRIs		
• Paroxetine	10 mg qd	20–50 mg
• Sertraline	25 mg qd	50–200 mg

Note that table applies to regular adult dosing. Pediatric and elderly dosing will be different, and may not be indicated. Qd, once daily.

Other medications have been studied, including the tricyclic antidepressants and MAOIs, 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 because 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 those that are targeted to the trauma itself. For example, uniform group therapies, that is, those that bring together people with shared traumatic experiences seem very effective. Effective therapies typically use exposure techniques, for example, exposing combat-related PTSD patients to sounds of gunfire, seem to help extinguish the associated fears. There is significant empirical support from controlled trials suggesting that specialized forms of CBT are effective (74–78). In addition, early aggressive treatment, particularly after the emergence of ASD, seems to help avert PTSD (79). For example, rapid interventions have been developed by the US militaries 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 reexperiencing, and high rates of dropout can be common. Therefore, management of factors that may influence dropout, such as excessive anxiety, should be used.

One controversial 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 practiced widely, EMDR has not shown greater benefit than other methods of psychotherapy, suggesting that the eye movements do not add additional benefit (80–82).

6.7. Clinical Course and Prognosis

The onset of ASD will be associated with recent trauma events. The course of ASD is self-limited, with symptoms lasting no longer than 4 weeks, although 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.

Full recovery is variable, and may or may not be dependent on treatment. There are instances of spontaneous remission without treatment, with estimates at approximately 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 to 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

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Abstract Obsessive–compulsive disorder (OCD) is the fourth most common neuropsychiatric disorder, with lifetime prevalence estimates of 0.4 to 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. OCD is postulated as a frontal–striatal disorder, and functional neuroimaging studies provide a strong support for the dysfunction of the cortico–striatal–thalamic–cortical neurocircuit. OCD can be secondary to a variety of medical conditions, which 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 cognitive–behavioral therapy (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 examines OCD from the medical perspective.

Keywords Autoimmune · Cortical–striatal–thalamo–cortical circuit · Genetics · Neuroimaging · Obsessive–compulsive disorder · Treatment

1. Introduction

As defined in DSM-IV, obsessive–compulsive disorder (OCD) is an anxiety disorder, 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, ordering and symmetry, and hoarding. Common compulsions include excessive cleaning, checking behaviors, ordering and arranging rituals, counting, repeating routine activities, and hoarding. 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 during the course of the illness, but those without a personal or family history of tics are more likely to have more frequent contamination themes.

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 (1–3). Approximately half of all OCD patients first present in childhood, before age 15 years (4), with biphasic symptom presentation at approximately age 10 years, and then again in early adulthood, with male patients presenting with an earlier onset. In adulthood, the proportion of affected men and women is approximately equal. In clinical samples, OCD seems more common in whites than African Americans. However, epidemiological data are conflicting, with one study suggesting no differences in prevalence as a function of ethnicity or geographic region (5) and another suggesting that the prevalence of OCD is significantly lower in African Americans and Hispanic Americans compared with whites (6). Minorities, particularly African Americans, are often underrepresented in research studies on OCD. It is unclear whether recruitment efforts geared to African Americans have been inadequate (e.g., not culturally sensitive) or whether the prevalence of OCD is actually lower in this population. The clinical course of OCD is often described as chronic and unremitting. The proportion of patients having a chronic course has been reported as ranging from 44 to 84% (7, 8), whereas the proportion of patients having an episodic course of OCD was only 5 to 10% (8, 9). That some cases of OCD can show an episodic course is less well-recognized (10). In studies on the course of OCD

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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% (11); however, in studies of clinical adolescents, the majority had some symptoms and remained on medication 2 to 7 years later (12–14). Factors that contribute to a more benign course include the presence of precipitating event, episodic nature of the symptoms, and good social/occupational adjustment (15, 16). 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 (8, 13, 16, 17). Once OCD becomes entrenched in the daily lives of those affected (because of 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 of 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 (18), to the degree that functionality is impaired. Obsessional thoughts centered on the loved ones are proposed to contribute to the social networks needed for the maintaining of the human race (19). 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 (20, 21).

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 (22). 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 (GP_i) and substantia nigra (SN_r) to the thalamus, and, in turn, back to the 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 the thalamus back to the same cortical region. Cognitive and emotional processes are handled by CSTC loops that 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. Neuroimaging studies also support the dysfunction of CSTC neurocircuit in OCD. Environmental, genetic, and clinical factors interact in a complex fashion in the individual patient. This chapter examines OCD from the medical perspective.

3. Neuropsychiatric Disorders Frequently Comorbid with OCD

In early onset OCD, comorbid psychiatric disorders are present in approximately 80% of 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% of patients (23). 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 symmetrical or even on each side). In adults, lifetime comorbidity of major depression is reported to range from 32 to 78%, and the comorbidity of other anxiety disorders, such as specific phobia, panic disorder, generalized anxiety disorder, and social phobia ranges from 14 to 54% (24). 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 (25). This high level of comorbidity (which is more evident in early onset OCD) suggests that the underlying relationship between OCD and other disorders is nonspecific or is caused by overlapping neurophysiology of central nervous system (CNS) dysfunction.

4. Genetics of OCD

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 (26–30). First-degree relatives of OCD probands were approximately six times more likely to have OCD, compared with control relatives, and

OCD was more common in relatives of probands with early age of onset, compared with adult onset probands (28,30–32). A meta-analysis of data from five family studies with OCD probands revealed a summary odds ratio (OR) of 4.0 (95% confidence interval [CI], 2.2–7.1) for OCD in the first-degree relatives (33). 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 (34). Increased rates of tics among first-degree relatives of OCD probands (35) as well as increased rates of OCD among first-degree relatives of TS probands (36) suggest that some cases of OCD may share the same genetic origin as tic disorders (35, 36). Interestingly, the younger age at onset of OCD symptoms and possibly male sex were associated with increased tic disorders in relatives (35).

Since Lange published the first cases of twins with OCD in 1929 (37), numerous twin studies have shown elevated concordance (80–87%) among monozygotic (MZ) twin pairs compared with dizygotic (DZ) twin pairs (47–50%) (38, 39). The heritability estimates were 44% for obsessive–compulsive traits and 47% for OCS in a study with 419 twin pairs (40).

Several complex segregation analyses were performed to investigate the mode of inheritance. The results support the existence of genes that have major effects on the transmission of OCD (41–43). A complex segregation analysis of OCD in 153 families (80 case and 73 control families) found the evidence consistent with involvement of a dominant or codominant gene or genes of major effect, especially in families ascertained through a female proband (44). 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 (45). However, Mendelian factors only partially explained the familial aggregation of the phenotype, and residual familial effects were necessary to adequately fit the data, which implies polygenic factors may also contribute to the etiology of OCD (44, 45).

Because of the strong genetic component, there have been efforts to identify the susceptibility genes by means of whole genome linkage analyses and candidate gene studies. Two genome-wide scans of OCD have been published (46, 47). In the first genome-wide scan (44), seven pedigrees (56 subjects) that had pediatric probands with OCD and at least two affected relatives were genotyped, using an 11.3-cM microsatellite marker map, and the initial findings on 2q, 9p, and 16q were followed up by genotyping additional markers in the original subjects plus 10 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 (48). Interestingly, a glutamate transporter gene (*SLC1A1*) that encodes excitatory amino acid transporter 3 (EAAT3) resides in this 9p24 chromosomal region, and two groups recently reported an association between this gene and OCD (49, 50). The second genome-wide scan was performed in 219 families at an approximate density of 9 cM, and found suggestive signals from chromosome 3q, 7p, 1q, 15q, and 6q (47). This group is currently pursuing fine mapping in these regions, with particular focus on 3q27-28.

A large number of candidate gene studies of OCD have been published. These have focused primarily on the serotonergic and dopaminergic system-related genes, such as genes encoding serotonin receptor/transporter, dopamine receptor/transporter, catechol-O-methyltransferase (COMT), and monoamine oxidase A (MAOA). For the serotonin system, serotonin 1B receptor (*5HT1B*), serotonin 2A receptor (*5HT2A*), serotonin transporter (*SLC6A4*), and tryptophan hydroxylase 1 (*TPH1*) were studied for association, but, except for *5HT2A*, the negative results outweighed the positive findings (51–59). The dopamine receptor types 2, 3, and 4 (*DRD2*, *DRD3*, and *DRD4*) and dopamine transporter (*DAT1*) genes were investigated (60–62), and the positive association was only replicated for a 48-bp repeat in exon 3 of *DRD4* (60–63). For *COMT*, Val158Met polymorphism has been studied by several groups using both case–control and family-based association methods, with mixed results (34). Finally, two groups have reported an association between the *MAOA* gene (64, 65) and OCD. Interestingly, they also found a sexually dimorphic effect of *MAOA* on genetic susceptibility to OCD. As mentioned above, in this section, an association between a glutamate transporter gene that encodes EAAT3 (*SLC1A1*) and OCD was reported by two independent groups (47, 48). Glutamate system genes warrant further investigation as functional candidates for OCD, based on the following lines of evidence: 1) elevated glutamate levels in several brain regions in OCD patients were observed in recent magnetic resonance spectroscopy (MRS) studies (66–68), and 2) the corticostriatal glutamatergic system has been reported to mediate spontaneous stereotypic behavior in mice (69). In addition, genes involved in immune response, such as genes encoding toll-like receptor 2 (TLR-2), forkhead Box P3 (FoxP3), caspase recruitment domain-containing protein 15 (CARD15 or NOD2) and myelin oligodendrocyte glycoprotein (MOG) may warrant investigation as candidate genes for OCD, because of identification of a subgroup of children, described by the term pediatric autoimmune neuropsychiatric disorder associated with streptococcal infections (PANDAS), with onset of OCD symptoms after streptococcal infections. Interestingly, a family-based association study reported an association between a polymorphism in *MOG* and OCD (70).

Additionally, the existing animal models of OCD, such as the Hoxb8^{lox} mutant mouse (71), DICT-7 transgenic mouse (72), DAT1 knock-out mouse (73), and 5HT2C receptor knock-out mouse (74), would be very useful in identifying specific genes and neurobiologic pathways involved in the pathogenesis of OCD. However, the question of whether the

behavior is a direct result of the specific gene or caused by the other downstream events may still remain (75).

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 studies have not confirmed any susceptibility locus yet, probably because of phenotypic and genetic heterogeneity. A number of candidate gene studies were conducted for association, with mixed results. The genes that warrant further replication, however, include *5HT2A*, *DRD4*, and *MAOA*. The positive results from the two interesting candidate genes, *SLC1A1* and *MOG*, encourage further investigation of glutamate system and immune response-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 will ultimately lead to locating genes that confer risk to OCD (76).

5. Neuroimaging Studies

Although not always consistent, structural magnetic resonance imaging (MRI) brain scan studies have suggested basal ganglia and frontal pathology, such as reduced volume of bilateral orbitofrontal and amygdala, absence of the normal hemispheric asymmetry of the hippocampus–amygdala complex, and decreased caudate volume in patients with OCD (77–79). In studies investigating brain structures in medication-naïve children with OCD, significantly smaller striatal volume, larger ventricles, and a larger corpus callosum were observed (80, 81). In addition, the size of the corpus callosum was correlated significantly with OCD symptom severity, and age-related increases in callosal size seen in healthy subjects were absent in OCD patients (80). The significance of corpus callosum differences in OCD was further supported by case reports of OCD patients with hypoplasia of the corpus callosum (82).

Functional neuroimaging studies also revealed dysfunction in the orbitofrontal cortex and basal ganglia in individuals with OCD (18). Fluorodeoxyglucose (FDG) positron emission tomography (PET) studies showed increased glucose metabolism in the orbitofrontal cortex, caudate, thalamus, prefrontal cortex (PFC), and anterior cingulate gyrus (83). Subsequently, changes of regional brain metabolism were examined in patients after behavioral or pharmacologic treatment, and showed decreased (normalized) caudate and frontoorbital metabolism (84–86). Furthermore, reductions in regional cerebral blood flow measurements in the frontal cortex, left temporal cortex, left parietal cortex, right caudate nucleus, and right thalamus were found in a single-photon emission computed tomography (SPECT) study (87), and decreased levels of *N*-acetyl-L-aspartate (NAA) in striatum and anterior cingulate were seen in studies using MRS (88,89). In a subsequent study using MRS, elevated glutamate levels in the bilateral caudate nucleus in 11 drug-naïve pediatric subjects with OCD were normalized after pharmacologic treatment (90). In addition, OCD patients seemed 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 idea of corticostriatal dysfunction in OCD.

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 (91–93).

Recently, a few studies have examined the neural correlates of the OCD symptom dimensions using functional neuroimaging techniques (22, 93, 94). For example, cerebral blood flow in the striatum was increased with checking symptoms and decreased with symmetry/ordering symptoms, whereas washing symptoms correlated with increased cerebral blood flow in the bilateral anterior cingulate and left orbitofrontal cortex in a study using PET (94). In another study using functional MRI (fMRI) with symptom provocation paradigm, bilateral ventromedial prefrontal regions and the right caudate nucleus correlated with washing; the putamen/globus pallidus, thalamus, and dorsal cortical areas correlated with checking; the left precentral gyrus and right orbitofrontal cortex correlated with hoarding; and the left occipitotemporal regions correlated with aversive, symptom-unrelated provocation (95). Taken together, contamination/washing and hoarding symptom dimensions seem predominantly mediated by limbic regions, whereas the checking and symmetry/ordering dimensions seem predominantly mediated by frontostriatal regions (22).

In addition, neuroimaging studies suggest that right hemisphere structures are more frequently or more dramatically involved than are left hemisphere structures (96–98). 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 (99, 100).

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 (22).

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. Research in adults 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 control subjects (101), whereas another study showed no differences (102), suggesting these findings may relate more to the symptoms rather than vice versa.

Reduced verbal and design fluency in patients with OCD was found when compared with control subjects, with evidence of a correlation between severity of OCD symptoms and design fluency (103). Additionally, patients with OCD may have nonverbal and praxic memory deficits, which may represent the cognitive substrate of doubt-related phenomena such as checking (104).

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, suggesting deficits in nonverbal memory (105, 106) perhaps based on poor strategy selection in reproducing the figure (105). 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 many fewer studies exist. 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 control subjects on an array of neuropsychological tests (107, 108).

7. OCD Induced by Psychological Trauma

Early stressful events (disruption of social environment secondary to moves, illnesses, etc.) have been associated with the onset of OCD in some cases. More than 50% of children and adolescents cite a precipitating event (109). Prolonged exposure to stress and trauma are theorized to increase the hypersensitivity to perceived threats leading to OCD symptoms (110). The relationship between OCD and posttraumatic stress disorder (PTSD) found in clinical samples is likely caused by symptom overlap between the disorders as well as comorbid depression (111).

8. Structural Brain Etiologies of OCD

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 traumatic brain injury (TBI), strokes, tumors, carbon monoxide poisoning, wasp sting necrosis, and manganese intoxication (112–116). 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 (113). Although the symptom presentation in these cases is similar to idiopathic OCD, because they are caused by a secondary condition, they are classified as "Anxiety Disorder due to (indicate the general medical condition) with obsessive–compulsive symptoms."

The rate of new onset OCD after TBI is unknown, although previous reports have placed the incidence at between 0.5 and 7.8% of brain injuries (117). Although symptoms that would meet full diagnostic criteria of OCD are relatively uncommon after 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 (117). The emergence of other psychiatric disorders is common as well. In one study examining the new onset of psychiatric disorders in children after TBI, it was revealed that 76% of the subjects developed a new psychiatric disorder within 2 years of a head injury (118). In this particular study, one of the 50 patients with TBI went on to develop OCD (a rate of 2%) (118). Although it was once thought that long-term psychiatric and neurocognitive sequelae occur only with moderate or severe brain injuries, evidence that is more recent indicates that significant psychiatric sequelae, including OCD, can occur even in mild TBI (118, 119) and without any evidence of abnormalities on MRI or computed tomography (CT) scans (120, 121).

The incidence of new-onset OCD symptoms after 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 after 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 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

in which acquired OCD presents in the elderly population, it becomes more likely that there is an underlying medical cause for the OCD symptoms, because the rates of idiopathic OCD decline with advancing age (122), and rates of strokes and tumors increases. 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 years (123).

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 (112, 124–128). Corresponding SPECT data reveals areas of hyperperfusion or hypoperfusion, reflecting changes in function in these brain areas (112). 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 (112). It has been postulated that focal damage may cause a disruption in the circuitry, which then results in area of under use or compensatory over use in other parts of the circuit (129).

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 (130, 131) and frontal lobes (132) 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 (114, 124, 133–135), 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 OCS (136). Strokes affecting the parietal lobe (137) and the frontal lobe (112, 123, 138) have also been reported to precipitate OCD. After brain injury, the onset of OCS 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 (120). The onset of the OCD may or may not be related to psychological reaction related to the trauma (117, 139). In these cases of delayed onset of OCS, it is put forward that underlying structural damage done to the septo-hippocampal area from the brain injury then leaves the patient more susceptible to OCD in the face of ongoing psychological stressors (139). The nature of symptoms may change over time as well (126).

Similar to the case of TBI, the onset of OCS 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 OCS. In the case of tumors, the onset would likely be more insidious. In one case, a 16-year-old boy with a brain dysgerminoma affecting the left lenticular region and right internal capsule developed OCS, which then improved as the tumor was treated with chemotherapy. Changes in personality and the reappearance of OCS were early signs indicating the relapse of the tumor on several separate occasions. With each episode, the symptoms improved as the tumor was treated (130).

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 (117, 124). One study comparing idiopathic OCD, acquired OCD, and healthy control subjects across a variety of neuropsychological indices, reported that similar deficits in attention, memory, language, and executive functioning were seen in both of the OCD groups but not in the healthy control subjects (124).

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 (126, 140). 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 (141). This lack of anxiety has been reported in those patients with damage primarily to the basal ganglia (114).

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 OCS. For example, in one case, a cranioplasty was instrumental in the resolution of symptoms in a patient after TBI, and, in another case, chemotherapy successfully treated OCS caused by a dysgerminoma (130, 142). Several cases report on the benefits that specific patients have derived from selective serotonin reuptake inhibitors (SSRIs), including fluoxetine (112, 143). In one case, a patient with acquired OCD was successfully treated with 60 mg fluoxetine daily with a decrease in his Yale–Brown Obsessive Compulsive Scale (YBOCS) score from 30 to 10 during a 90-day period. In this case, there were multiple brain lesions shown on MRI scan, including injuries to the orbitofrontal cortex bilaterally; as well as low serotonin transporter density in the midbrain and hypothalamus shown on SPECT (144). Several authors have reported on the effectiveness of cognitive–behavioral therapy (CBT) in addition to treatment with medications (128, 134). In one case, a 78-year-old man who developed OCD after an infarct to the left basal ganglia had minimal response to SSRIs but achieved significant improvement after undergoing CBT in an intensive inpatient program. In this case, the patient's YBOCS score went from 24 to 2 with good maintenance up to a year after treatment (134). Another group reported on the combination of cognitive rehabilitation and CBT for a patient with a brain injury. In this case, memory problems after the injury led to obsessional checking, and it was important to work on implementing an external memory system as well as engaging in exposure/response prevention to treat the OCD symptoms (145). In some cases, improvements using standard treatments for OCD are ineffective. In one case, a patient who developed OCS after a frontal lobe infarct failed to respond to more than

TABLE 10.1. Medical aspects of OCD.

Structural brain	Stroke
	Tumor
	Parkinson's disease, other basal ganglia illnesses
	Head injury
	Morphology, e.g., caudate size, etc.
Immune illness	Sydenham's chorea
	Multiple sclerosis
	Systemic lupus erythematosus
	Acute disseminated encephalitis
	PANDAS
Neurochemical	Oxytocin, vasopressin
	Glutamate
	Serotonin
	γ-aminobutyric acid (GABA)
	Corticotropin-releasing factor (CRF)
	Dopamine
	Medication-induced OCD
Psychological	Trauma
	Accommodation
Neuropsychological	Neurological soft signs
	Visual memory
	Executive function
Medical manifestations of OCD	Dermatologic
	Food restriction

35 different medications (123). 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 decreased processing speed caused by a neurological deficit versus obsessional slowness, or perseveration that is often seen in brain injuries versus OCS. In addition, patients may be reticent to report OCS 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 (see Table 10.1).

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 erythematosus (SLE) (146), multiple sclerosis (MS) (147, 148), and acute disseminated encephalopathy (149). Another group reported a 10- to 15-fold increase in OCD in patients with SLE when compared with rates in community-based samples of OCD (146). Similarly, others have shown a higher than expected rate of OCD in patients with MS (148) and thyroid dysfunction (150). On the other hand, evidence from a chart review (110) showed higher than expected rates of immune-related disease in psychiatric patients with OCD when compared with 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 (18, 151). 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 (152). Although it is not as striking, an increased incidence of OCD in rheumatic fever (RF) without chorea exists (153), occurring only during acute episodes of RF. One study looked at adults with a history of RF or diabetes and found that there was no difference in OCS in either group (154).

During the past several years, significant strides have been made to characterize the association of OCD and tics with GAS, a syndrome called PANDAS. The current definition of PANDAS includes the presence of OCD and/or tic symptoms with onset during the prepubertal years, which is episodic or sawtooth in its course, occurs in association with GAS infection, and presents with neurological findings (155). These cases often present at an early age with an acute appearance of symptoms. The onset or exacerbation of OCD and/or tic symptoms often follows an episode of streptococcal pharyngitis.

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 (156). After that initial report, there have been many case reports, and more recently, case series further elucidating this phenomenon (155, 157–164). Some complications exist in attempting to investigate these cases. In many cases of streptococcal infections, symptoms are subclinical and will, therefore, miss detection (165). In RF, an illness that is clearly associated with streptococcal infections, one study reported that in upward of 75% of cases, the onset of symptoms occurred with minimal or no evidence of a preceding case of pharyngitis (166). Further complicating the ability to establish a definitive GAS link to OCD symptoms, is the observation that elevated streptococcal titers are common in the prepubertal age group (167), therefore, a single elevated titer in a child with new-onset OCD would not imply a causal relationship with an infection. 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 OCS or tic symptoms. Some children with tics and OCD, similar to reports in RF (168), may have persistent immune activation to GAS. 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 streptococcal titers compared with those who had a course inconsistent with PANDAS (169). This finding may be caused by the relative proximity of the streptococcal infection at the time of study enrollment, and then by 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, as reported by other investigators (157, 170–172).

Frequent GAS infections may also predispose children to neuropsychiatric sequelae (173). Reasons for GAS recurrence are likely complex and numerous. Most of the recurrences are relapses, in other words, infection by the same streptococcal type, as opposed to new infections of a different type (174). Possible reasons for relapse could include poor compliance or inadequate duration of antibiotic therapy, poor antibiotic penetration into tonsillar tissue, inactivation of antibiotic caused by β-lactamase-producing bacteria, lack of protective oral flora, reexposure, or immunological defects (175). The consequences of recurrent tonsillopharyngitis are largely unknown. Many OCD or tic patients report onset of their neuropsychiatric symptoms after repeated streptococcal infections during the course of a few months (TK Murphy, unpublished data, 2006). Published support for the risk associated with repeat GAS infections includes a recent epidemiologic study that used population-based data from a large health maintenance organization (173) and found that patients with OCD or TS were more likely than control subjects to have had streptococcal infection in the 3 months before the OCD or TS onset date. Having multiple GAS infections within a 12-month period was associated with a markedly increased risk for TS (OR, 13.6) (173). The number of previous GAS infections has been shown to correlate with a more severe course and a greater incidence of relapse (161). A school study that examined motor 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 (176). Further complications occur because 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 streptococci (177), allowing these strains to activate the immune system without being detected by standard culturing techniques. Conversely, group C and G streptococcus may cause false-positive results, because these strains may lead to elevation in streptococcal titers without causing a corresponding increase in OCD symptoms (169).

Seasonal variations are often seen in autoimmune illnesses (178). For example, the peak incidence of RF is from January to March, which lags the peak incidence of GAS by a short period (179). In addition, RF 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 (169, 180). 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 (171, 172). It is possible that some individuals have a heightened susceptibility to OCD or tics that are triggered by these other factors rather than GAS.

There are various theories regarding how streptococcal infections may cause OCD or 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 CNS, 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 SC is potentially helpful. In SC, there is a well-characterized rise in antibasal ganglia antibodies (ABGA) to the caudate (181). Similarly, AGBA have been observed in patients with TS (159, 182). Despite the presence of some positive studies, there are also several studies using different techniques and epitopes that show minimal differences in antibody binding when comparing patients with OCD or tics with control subjects (183–186). 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 (183–186). 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 (187–189).

Although 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 (190–193). Some studies have shown abnormalities in immune function in adults with OCD (191, 194), although other studies have not found this (190, 193, 195, 196). The need for further investigation is emphasized by the mixed results of adult OCD immune function studies, the small sample sizes, and the lack of evidence to determine the relative contribution of alterations in the hypothalamic–pituitary–adrenal (HPA) axis caused by 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 (197–202).

10. Medication-Induced OCS

Certain pharmacologic agents, such as methylphenidate/dextroamphetamine (203), zonisamide (204), and m-chlorophenylpiperazine (m-CPP) (205), have been reported to trigger OCS. In addition, worsening or de novo production of OCS related to the use of atypical antipsychotics has been documented in numerous case reports, despite their anti-obsessional effects in OCD (206). 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 (207). There has been no case report of OCS related to the use of aripiprazole or ziprasidone yet. Interestingly, all cases of antipsychotic-induced OCS have involved patients with primary psychotic disorders, mostly chronic schizophrenia, rather than pure OCD (206). In most cases, OCS emerged 3 to 15 months after the medication was started and was of transient nature (206). Coadministration of a SSRI diminished OCS in some patients receiving clozapine (208). Given the higher affinity for serotonin 5HT2 receptors than dopamine D2 receptors at low dose, 5HT2 receptor antagonism has been postulated to play a role in atypical antipsychotic-related OCS, whereas anti-obsessional effects may occur through D2 receptor antagonism at higher dose (206, 209). 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 (209).

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 (210). In addition, the anti-obsessional effect of atypical antipsychotics may be more pronounced at higher does (209, 210).

11. Medical Consequences of OCD

It is well known that OCD can be very debilitating, limiting the patient's ability to work and maintain meaningful relationships, and affecting multiple quality of life areas. What has been less well documented are some of the potential medical consequences of OCD. The most clearly documented medical consequences of OCD involve dermatological problems. Several studies have been performed 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 previous diagnosis of OCD. In this study, they showed that the dermatologic diagnoses varied widely and were not necessarily directly related to OCD (211). Another study, focusing on pruritic dermatological conditions, found 14% of a randomly selected group of patients had OCD that had not been previously diagnosed (212). 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 6 had been previously diagnosed. In this study, the dermatological diagnoses were split into those that are possibly caused by psychological factors, including eczema, pruritis, urticaria, and psoriasis, and those that are unlikely to be caused by psychological causes. Interestingly, they found that there were no statistical differences in the psychological versus nonpsychological causes between the OCD and non-OCD groups (213). 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%). Although, in psychiatry clinics, patients with OCD often have dermatitis from excessive hand washing, use of chemical cleansers or neurotic excoriations, in the population of dermatology patients, the increased incidence of OCD seems to be unrelated to OCD symptoms or anxiety. Other dermatological sequelae from OCD can include excessive skin picking and lip licking, as well as related problems, including trichotillomania and nail biting. Cases of pica have been reported to be secondary to OCD (214).

Other potential medical consequences that may be caused by OCD include those related to food refusal and decreased motor movements. There have been cases in which patients have refused to eat and lost enough weight that placement of a gastric feeding tube was 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 (215). 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 (216,217). Patients who refuse to get out of bed may develop bedsores and orthostasis and general weakness over time. Although these are clearly rare and exceptional risks of OCD, they have been noted and are worthy of consideration.

12. Treatment

12.1. Behavioral

CBT for OCD is a structured approach to teaching skills for responding to symptoms. The efficacy of CBT has been

supported in clinical trials and CBT has shown excellent maintenance of symptom reduction at follow-up (218–220). 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.

12.2. Pharmacological Treatment

Although 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 (219, 221). 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. Although the role of the 5-HT system seems to be more important in the treatment than in the etiopathology of OCD, more direct measures of neurochemical dysfunction, including paradigms that use biological markers, pharmacologic challenges, or functional neuroimaging, are needed to corroborate the pathophysiologic role for 5-HT.

Acute blockade of 5-HT reuptake seems to be the critical first step in a chain of neural events leading to efficacy in the treatment of OCD. It is thought 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 (222). 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 (223). In contrast, the PFC, thought to be the main target in the treatment of OCD, does not undergo desensitization for up to 8 weeks (223). 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 (224). 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. 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 (225). In adults, response rates for SSRIs and CMI have been reported to be between 40 and 60% of participants, compared with less than 20% for placebo (226). CMI and SSRIs consistently show superiority over placebo in the treatment of OCD symptoms (227–232). In meta-analyses of CMI compared with other SSRIs, CMI continues to show better efficacy than any single SSRI or SSRIs as a pooled group in both children and adults (226, 233, 234), although this superiority has not been shown in individual trials comparing CMI directly with fluvoxamine, paroxetine, or fluoxetine (226). No clear differences in efficacy have been shown when comparing any single SSRI with another, and it is generally accepted that, except for possibly CMI, all SSRIs are essentially equally effective.

Despite the superiority of CMI in these studies, CMI 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 thought to be a first-line agent. Instead, SSRIs are considered first-line medications in this disorder (235). 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 versus 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 (236).

Once a medication choice has been made, it is important to address several important issues in the treatment of OCD. First, 10 to 12 weeks at adequate dosage is necessary to evaluate the efficacy of the medication. It is generally accepted that if one SSRI fails, a second SSRI should be tried, because 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. Although there are few studies looking at continuation of medication after improvement of symptoms, it is thought that ongoing administration of the medication at the treatment dose will be necessary for at least 1 to 2 years after the improvement in

symptoms before tapering and discontinuing the medication to minimize risk of relapse. However, some patients need to be maintained on their medication for several years.

Many augmentation strategies have been attempted in the treatment of OCD. 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 (237–239), buspirone (240–242), and clonazepam (243) 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 lead 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 (244) and haloperidol (245, 246), 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 (246–249), although differences were not seen in the benefits for patients with comorbid tics or schizotypal personality disorder when compared with patients without these comorbidities. Studies have shown mixed results with augmentation of quetiapine, with some studies showing benefit (250, 251), whereas other studies showed no statistically significant improvements over placebo (252, 253). 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 (254), whereas a second study showed significant improvement in OCD symptoms after the addition of olanzapine (255). Aripiprazole is perhaps one of the most promising augmentation strategies in need of further exploration (256, 257).

Dysfunction of glutamatergic neurotransmission has been implicated in the pathophysiology of OCD (50, 67, 258), and recent clinical reports suggest that some glutamate-modulating agents are efficacious in the treatment of this disorder (259, 260). An increased caudate glutamatergic signal was found in treatment-naïve children with OCD when examined by proton MRS (67). Furthermore, this elevated signal normalized after effective SSRI treatment. The precise mechanism of SSRI modulation on the glutamate signal is not known. Other agents, such as riluzole and *N*-acetylcysteine (NAC), may exert such a dampening effect on glutamate release. Both riluzole and NAC have shown efficacy in small studies in treating OCD. 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 (261, 262). The partial NMDA agonist, D-cycloserine, has been proposed to facilitate CBT of anxiety disorders; small studies, thus far, have had positive outcomes (263) and negative outcomes (264). The use of D-cycloserine with CBT in the treatment of OCD is in progress. Other agents with the potential to affect the glutamatergic system include β-lactam antibiotics (265), which may add an interesting dual action in children with PANDAS. Any agents affecting this system would have to be fairly selective for such neurons to avoid generalized adverse events caused by generalized attenuation of glutamate transmission.

In many patients, if OCD is comorbid with tics, bipolar disorder, or schizophrenia, a combination of medications is frequently required. Comorbidity often clearly affects a negative treatment response (266), as demonstrated in one pediatric trial. 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.

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. Brain stimulation techniques, such as electroconvulsive therapy (ECT), vagus nerve stimulation treatment (VNS), and repetitive transcranial magnetic stimulation (rTMS), have all been tried, with varying success, in treatment-refractory OCD. More recently, after progress made with Parkinson's disease, essential tremor, and dystonia, deep brain stimulation (DBS) is currently being performed in refractory OCD cases. DBS has the added benefits of very specific targeting of the regions likely involved in the neurocircuitry mediating OCS (such as the anterior limb of the internal capsule), and the reversibility of the procedure (removal of stimulator, clipping leads) (267).

12.4. Treatment Relevant to PANDAS

The current standard of care for PANDAS is the same as that for OCD and tic disorders; namely, treat with SSRI and/or CBT and follow the course of illness. Although novel treatments are being researched (i.e., prophylactic antibiotics, intravenous immunoglobulin, plasma exchange), it is imperative that the primary care physicians and parents continue the current standard of care and wait for results from large well-controlled clinical trials before rushing into higher-risk therapies. Antibiotic treatment of GAS infection has

not received adequate attention in the PANDAS literature; however, such treatment has been thoroughly studied among patients with RF.

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; and 6) they are increased 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 regarding frontal–striatal circuitry, it would seem that OCD is not the result of a single specific factor, such as too little serotonin, too much dopamine, or 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
Somatoform and Dissociative Disorders

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Abstract Most patients consulting physicians have a mixture of physical and mental complaints that require careful differential diagnosis. A somatoform disorder is diagnosed when the primary disorder is a mental disorder with prominent physical complaints. The assessment and treatment of somatoform disorders requires patience and compassion to maintain a therapeutic alliance, but randomized controlled trials show that treatment with antidepressants or cognitive–behavioral therapy reduce health care use and subjective distress.

Somatization disorder is the prototype of somatoform disorders. It has been shown to be a chronic and heritable deficit in emotional intelligence that is clinically manifest with complaints of multiple bodily pains, and gastrointestinal, pseudoneurological, sexual, and reproductive symptoms. Conversion disorders involve acute or chronic loss of voluntary sensorimotor functions, such as psychogenic blindness, paralysis, or tremors, in response to psychosocial stress, such as marital quarrels, personal rejection, or events associated with a high risk of injury or death. In contrast, some somatoform 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 such as 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 suggests 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.

Keywords Alexithymia · Brain-imaging · Conversion disorder · Dissociative disorders · Emotional intelligence · Meditation · Pharmacotherapy · Psychotherapy · Self-awareness · Somatization disorder · Somatoform disorders · Well being

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, therefore, 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). Patients with nonphysiological 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

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TABLE 11.1. DSM-IV-TR 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
Somatoform 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

mechanism, such as a medical condition associated with many somatic complaints such as hyperparathyroidism. 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, the distinction between psychological and physical disorders is not reliable in the vast majority of cases of somatoform disorders. The most common somatoform disorder in primary care is "undifferentiated somatoform disorder" which requires 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, or too indifferent; responds to suggestion or 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 nonspecific and transient improvement when they are relaxed (2). History of somatoform disorders predicts 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 (3–5). Personality disorders also vary widely in their association with somatoform disorders. Some character disorders are associated with a high risk of somatoform 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 intelligences of different aspects of our being (i.e., the body, the thoughts, and the psyche).

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.

TABLE 11.2. Usefulness of psychiatric criteria for distinguishing conversion and dissociative reactions from physical disorders.

	Putative diagnostic criteria	Predicts no physical disorder
History		
Somatization Disorder	Yes	
History of conversions	Yes	
History of somatic complaints	Yes	
Personality Disorder		
With history of somatoform disorder	Yes	
No history of somatoform disorder		No
Current presentation		
Current anxiety or dysphoria		No
Emotional stress before onset		No
Secondary gain		No
Partial improvement with suggestion or sedation		No
La belle indifference		No

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, although not treatment for the complaint that they are making. Even if a patient is judged to have a somatoform 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 (6). 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 their medical condition (to quote DSM-IV)—but 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 (7, 8). Personality traits such as Harm Avoidance predispose to anxiety, which, in turn, amplifies somatosensory perception and intensifies the experience of pain (9). The dualistic concept underlying the DSM classification of somatoform 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 all of these intelligences be integrated. The emotional intelligence of a person is a characteristic of the limbic system of their 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 complex and dynamic process that depends on the inseparable interplay of the body, the thoughts, and the spirit of the person as a whole (10).

Despite all of these problems with the 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, to understand somatoform 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 somatoform and dissociative disorders such as 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 to treat acute somatoform and dissociative disorders such as 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 somatoform or dissociative patients. Somatoform 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.

2. Emotional Drives and Emotional Intelligence

People differ markedly from one another in their emotional style. More than 2000 years ago, Aristotle recognized four temperaments that he attributed to the effects of different body humors: the melancholic (caused by melancholy or black bile), the choleric (caused by choler or yellow bile), the sanguine (caused by blood), and the phlegmatic (caused by phlegm). The four humors were body fluids considered 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 it 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 approximately one third of people being near average and the two extremes being designated as high or low scorers (11). These traits are all approximately equally influenced by individual differences in genetic factors and in variables unique to each individual

TABLE 11.3. Descriptors of individuals who score high and low on the four temperament dimensions as measured by the TCI.

Temperament dimension	Descriptors of extreme variants	
	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

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(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 (regulated by Harm Avoidance), anger (regulated by Novelty Seeking), disgust (regulated by Reward Dependence), and ambition (regulated 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, they will miss many opportunities that could have benefited them, but, at the same time, they are 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 their risk taking. For the extremes of Novelty Seeking, people who are highly impulsive will explore opportunities quickly but also may get into frequent fights because of their quick temper; people who are highly rigid will be orderly and conserve resources well, but have difficulty making inquiries and asserting themselves. For the extremes of Reward Dependence, a person who depends on external approval may make many friends but they are 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, which is shared with reptiles and mammals, and which evolved millions of years ago (12). People have the capacity to be come self-aware of their emotional reactions and feelings of relationship to one another by means of limbic cortical communication via the Papez circuit, which connects the anterior cingulate cortex (ACC) with the hypothalamus, thalamus, and hippocampus (13). The ACC provides a key interface for the regulation of emotional drives, cognition, and motor behavior (14). As a result, it plays a key role in contemporary neural models for the heterogeneous category of major depressive disorders (15). The size of the ACC and its functional connectivity with cortical and limbic structures is strongly moderated by temperament traits, particularly Harm Avoidance (16–18). 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, somatoform and dissociative disorders are associated with overactivity of the ACC and highly variable overactivity or underactivity of various parts of prefrontal cortex (1, 19).

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 (20, 21). 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) (22–24). People can be high in EQ and/or IQ, but not wise in a spiritual sense. Wisdom leads to a combination of creativity, well-being, and virtuous living, so wisdom supersedes 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 such as awe, humility, self-abnegation, reverence, and compassion, described in more detail later in Table 11.4. 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 psyche. 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 somatoform and dissociative disorders is increased. Therefore, to understand the etiology and treatment of somatoform and dissociative disorders, we need a fuller description of deficits in emotional intelligence.

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 (25, 26). 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 regarding the understanding and regulation of emotions.

The syndrome was first described when Peter Sifneos and John Nemiah observed that many of their patients with somatoform 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 (27). 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 somatoform and dissociative disorders more than other mental or physical disorders (26, 28–32).

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 (10). 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 such as awe and compassion (in the spiritual plane). The corresponding content of these planes for thought and for the psyche is described elsewhere (10), but, in discussing somatoform 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 (33). 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) (10). The strongest relations are between the TAS subscale for externally oriented thinking and the TCI scale for sexual aspects of Self-transcendence (self-forgetfulness). Such individuals are slow to become self-aware of physical sensations (34).

People with alexithymia are also at higher risk for somatoform disorders, substance dependence, depression, and particular psychosomatic disorders, such as hypertension, irritable bowel syndrome, and fibromyalgia (26, 35). For example, patients with fibromyalgia are higher in alexithymia and have greater anxiety and inwardly directed anger than healthy control subjects (35). Such findings suggest that alexithymic patients 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. Not knowing the emotional significance or cause of the sensations, somatoform 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.

TABLE 11.4. Features of alexithymia grouped according to planes of self-awareness.

Plane of awareness	Abnormalities observed in alexithymic patients
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

From reference (10).

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 problems in chronic somatoform and dissociative disorders. Treatment recommendations are sometimes made for a complex protocol in which it is unclear what is being done and for whom. Some forms of cognitive–behavioral therapy (CBT) or eye movement desensitization and reprocessing (EMDR) may be useful for some symptoms of some somatoform patients, but it is unclear what therapeutic elements are useful for particular symptoms of particular patients. In the past treatment of somatoform patients, results have been often been incomplete, with much refusal of psychiatric treatment, frequent drop-out, and weak to moderate results in those retained (1, 36, 37). 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 somatoform disorders (36). 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, such as what has long been done in Ayurvedic medicine (38). Training in nonviolent assertive communication can be explained in a concrete way to facilitate more effective self-expression (39). 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 (40). A DVD series has also been developed to teach an understanding of emotional processes and specific meditations that enhance sensory awareness, appreciation of beauty, empathy, and the principles of well-being (41). The DVDs for promoting well-being are designed with beautiful music and imagery to calm the emotional brain and allow self-paced assimilation of the dialog. There are an accompanying manual and workbooks for homework assignments, which make the materials suitable for everyone, including individuals with deficits in any form of self-awareness, including alexithymic patients and chronic somatoform 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 those with

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.

Indicators of elevated body self-awareness	Methods for elevating body self-awareness
Sexual plane	
Fluid and expressive body movement	Gymnastics, accupressure 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
Nonviolent 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 regarding 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 in Nature meditation
Abnegation of self	
Respect and compassion for others	Personal engagement in self-transcendent activities
Reverence for sacred things	

Adapted from the manual for The Happy Life: Voyages to Well-Being (41), with permission of the author and the Anthropaideia Foundation. Materials for treatment and training regarding these methods are available for those interested (see nonprofit websites at http://psychobiology.wustl.edu and http://aidwellbeing.org).

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, therefore 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 (42). 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 (43). 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 (44). In addition, the Union in Nature meditation from the Voyages to Well-Being is particularly useful but needs to be practiced for 30 minutes at least three times daily after mental trauma such as those typically associated with acute conversions or fugues to allow de-stressing of the limbic system (10, 41). This meditation is a means of enhancing sensory awareness to bring satisfaction and joy from everyday natural experiences of everyday life, such as walking, eating, smelling, hearing, and seeing. Detailed recommendations regarding choice of medications that are useful for target symptoms in somatoform and dissociative disorders, such as somatic anxiety, are described in Chapter 28 on personality disorders.

Until now, we have presented a flexible target-symptom approach to somatoform 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-IV. 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.

TABLE 11.6. Experiential methods for elevating the body component of thought in acute somatoform 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 nonjudging 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 three times a day
	Engagement in self-transcendent activities
	Voyages to Well-Being DVDs[a]

[a]DVDs available for use in clinician's self-training and in treatment (see http://aidwellbeing.org).

4. Somatization Disorder (Briquet's Syndrome)

Somatization Disorder is the prototype of all somatoform 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 such as 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 caused by 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 now disproven concept from ancient Greece that a wandering uterus caused pains in different parts of the body. Eli Robins and Sam Guze developed the modern description of the syndrome and validated it rigorously by follow-up and family studies (45). 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). Young adult women usually presented with the disorder but the 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 seems more typical of people who lived approximately 3,000 years ago than 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 (46).

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 (47), therefore, Guze suggested the label of Briquet's syndrome to distinguish the syndrome from histrionic personality disorders and acute conversion reactions. Guze's criteria were well validated but were cumbersome, requiring endorsement of more than 20 out of 59 possible symptoms of Briquet's syndrome, distributed in at least 9 of 10 empirically derived groups. As a result, few people used the research criteria in clinical practice.

TABLE 11.7. Diagnostic criteria for Somatization Disorder (DSM-IV).

A. A history of many physical complaints beginning before age 30 years that occur during a period of several years and result in treatment being sought or significant impairment in social, occupational, or other important areas of functioning
B. Each of the following criteria have been met, with individual symptoms occurring at any time during the course of the disturbance:
   1) *Four pain symptoms*: a history of pain related to at least four different sites or functions (e.g., head, abdomen, back, joints, extremities, chest, rectum, during menstruation, during sexual intercourse, or during urination)
   2) *Two gastrointestinal symptoms*: a history of at least two gastrointestinal symptoms other than pain (e.g., nausea, bloating, vomiting other than during pregnancy, diarrhea, or intolerance of several different foods)
   3) *One sexual symptom*: a history of at least one sexual or reproductive symptom other than pain (e.g., sexual indifference, erectile or ejaculatory dysfunction, irregular menses, excessive menstrual bleeding, vomiting during pregnancy)
   4) *One pseudoneurological symptom*: a history of at least one symptom or deficit suggesting a neurological condition not limited to pain (conversion symptoms such as impaired coordination or balance, paralysis or localized weakness, difficulty swallowing or lump in throat, aphonia, urinary retention, hallucinations, loss of touch or pain sensation, double vision, blindness, deafness, seizures; dissociative symptoms such as amnesia; or loss of consciousness other than fainting)
C. Either (1) or (2):
   1) After appropriate investigation, each of the symptoms in Criterion B cannot be fully explained by a known general medical condition or the direct effects of a substance (e.g., a drug of abuse, a medication)
   2) When there is a related general medical condition, the physical complaints or resulting social or occupational impairment are in excess of what would be expected from the history, physical examination, or laboratory findings
D. The symptoms are not intentionally produced or feigned (as in Factitious Disorders or Malingering)

Reprinted with permission from reference (64).

The widespread nature of the syndrome and its heritability were confirmed in adoption studies conducted in Sweden (48). Somatoform 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 somatoform 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 current DSM criteria using the same methods he had developed in the Swedish adoption studies (2). 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 (see Table 11.7). 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 (2). 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 CBT. 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 somatoform patient's physicians to be educated regarding 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).

Traditional ways of treating Somatization Disorder begin with particular attention to the way the diagnosis and a therapeutic alliance are established. Patients with Somatization Disorder are reassured when their physician takes the time to collect a thorough history, obtain medical records, and obtain 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 also require treatment. It is useful to assess personality with a questionnaire with internal validity controls, such as the TCI, particularly because this is prescriptive of treatment targets, as described in the Chapter 28 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, thus, there is a wide range of possible goals. The possible goals include at least education to help reduce excessive health care use and exposure to unnecessary tests and procedures, as is often done by providing consultation to their primary care physician (49). It can also include pharmacotherapy for target symptoms of somatic anxiety, depression, impulsivity, emotional detachment, and cognitive distortion, as described in Chapter 28 on personality disorders. Specific studies evaluating such pharmacological treatments in Somatization Disorder are detailed elsewhere (36). CBT 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% (50). A later randomized trial of CBT showed that it can produce moderate but clinically meaningful reductions in health care use and subjective complaints for approximately a year after treatment, even though it does not correct underlying deficits in emotional intelligence (51). However, relapse and recurrence are major problems for treatments such as CBT that do not correct the underlying deficits in emotional intelligence of patients with somatoform disorders (52). More ambitious work, still unproven by randomized controlled trials, includes efforts focused on the habilitation of emotional intelligence, as described in section 3.

5. Undifferentiated Somatoform Disorder

Undifferentiated somatoform disorder (USD) is really only a symptom, not even a syndrome. The diagnosis requires only one unexplained but persistent physical complaint, such as fatigue, loss of appetite, constipation, painful menses, or painful urination. The complaint must have persisted for 6 months or longer without a full medical explanation and cause significant distress or impairment. It cannot be explained by another mental disorder, such as Somatization Disorder or

disorders of mood or anxiety. It is not supposed to be intentionally produced or feigned. Unfortunately, the course of such individual unexplained physical complaints are unpredictable. When based on a single unexplained symptom, the diagnosis is useful primarily for actuarial and billing purposes, and has little or no validity for description, prognosis, or treatment.

Even when there are multiple unexplained somatic complaints, there is little information regarding 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) (53). Treatments did provide modest benefits compared with controls, but there was no differential effect of diagnosis or type of treatment.

6. Conversion Disorders

A conversion disorder is a medically unexplained loss or alteration in voluntary sensorimotor functions. The classic examples of conversion disorders are sensorimotor abnormalities that mimic neurological disorders, therefore, they often require coordinated evaluation and treatment with a neurologist 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. However, if the only sensory complaint is pain, then DSM-IV requires a diagnosis of Pain Disorder, not Conversion Disorder. Any of these sensory deficits or alterations besides pain is designated in DSM-IV as "Conversion disorder with sensory symptom or deficit."

Other common examples of conversion disorders are called "Conversion disorder with motor symptom or deficit." 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 dystonia; 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%) (54). 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 convulsions." 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, therefore, the diagnosis of such patients can be challenging. The key distinction is that conversion disorders involve some voluntary sensorimotor signs and symptoms mimicking a seizure (54).

Still other people present symptoms of more than one category of conversion and are designated as "Conversion Disorder with mixed presentation" in DSM-IV. 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.

No specific laboratory tests or signs on physical examination 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. In addition, 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 requires positive evidence of psychological factors that are judged to be associated with the medically unexplained symptom or deficit.

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 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 in section 3. For example, hyperactivity of the ACC has been suggested to actively inhibit motor activity in psychogenic paralysis (55). Hence, treatments are directed acutely at emotional appeasement of the emotional brain, as described in Table 11.6. 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 Table 11.5 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, 37) .

7. Other Somatoform Disorders

The somatoform cluster in DSM-IV also includes a heterogeneous collection of disorders, including pain disorders, hypochondriasis, body dysmorphic disorder (BDD), and others such as pseudocyesis that are not otherwise specified. These conditions involve diverse mechanisms and principles and some are unrelated to Somatization Disorder. As a result, we focus mainly on differential diagnosis with brief comments regarding 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. Pain Disorders may involve psychological factors, a general medical condition, or both. 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 caused by a general medical condition are diagnosed on Axis III.

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, many patients with pain disorder are alexithymic, which predisposes to complaints about pain (29, 56). In these pain patients, the same treatment approach is indicated as described earlier for improving emotional regulation in alexithymic patients.

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 (57). 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 (58). BDD is associated with severe anxiety and frequent suicide attempts. Clinically, BDD seems to be more closely related to social phobia and obsessive–compulsive disorder (OCD) 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 CBT such as 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 nineteenth century, hypochondriasis was associated specifically with complaints involving the "hypochondriac" region of the abdomen—that is, below the costal cartilages—rather than with regionally nonspecific morbid disease preoccupation (48). The DSM-IV criteria are essentially the same as proposed by Gillespie in 1928, who thought that hypochondriasis was an independent, discrete disease entity (59). Others concluded that hypochondriasis was always a secondary part of another syndrome, usually a depressive disorder (60). Studies that are more recent confirm that patients with hypochondriasis frequently have other cooccurring mental disorders, particularly anxiety and depressive disorders.

Hypochondriacs have an increased history of serious childhood illnesses and experience with disease in family members. These patients are often highly verbal and aware of the 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 (61). 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, CBT, or psychodynamic therapy.

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 (DID; formerly called Multiple Personality Disorder). Dissociative amnesia is a disruption of memory: specifically, it is the inability to recall important personal information in excess of what can be 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. 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 regarding 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. 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.

DID and Somatization Disorder are both chronic conditions, thus, 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, thus, they are sometimes grouped together as acute hysteria (55). 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 use of groupings based on course; acute hysteria, whether a conversion or dissociative disorder, is most consistently associated with hyperactivation of the ACC (55). Essentially stress activates the limbic system, and the ACC 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 (62). In contrast, Freud suggested that there was an active process by which disturbing mental associations were removed from conscious awareness (63). 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 ACC 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 somatoform 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

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Abstract The most widespread eating disorders, anorexia nervosa and bulimia nervosa, are potentially serious disorders with high morbidity and mortality primarily affecting young women. 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 anorexia nervosa, to define effective treatments.

Keywords Anorexia · Binge eating · Binge–purge · Bulimia · Eating disorders

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 that impairs social function or physical health significantly, but is not caused by a medical or other psychiatric disorder. The most widely recognized eating disorders, anorexia nervosa and bulimia nervosa, are common, potentially serious disorders that primarily affect young women. Both disorders are characterized by peculiar attitudes and behaviors directed toward eating and weight accompanied by intense weight loss. Anorexia nervosa is further characterized by obsessive pursuit of extreme thinness leading to emaciation, disturbance of body image, and, in female patients, amenorrhea.

The cardinal feature of bulimia nervosa is eating binges: 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 weight gain. However, bulimia nervosa does not produce the emaciation that accompanies anorexia nervosa.

Although anorexia nervosa and bulimia nervosa 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. In addition, there are similarities in many of the important characteristics of the disorders (Table 12.1).

The specific etiology of anorexia nervosa and bulimia nervosa is elusive and still unknown, although the genesis seems to be multifactorial, with the vulnerability to anorexia nervosa and bulimia nervosa 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 anorexia nervosa 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, whereas failure to eat or weight loss serves to avoid anxiety (1). Crisp (2) has postulated that a weight phobia springs from an 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.

1.1. Environmental Factors

Many of the same environmental factors that predispose to the development of anorexia nervosa are risk factors for bulimia nervosa. Sociocultural 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 anorexia nervosa and bulimia nervosa, particularly among vulnerable adolescents, who equate weight control and thinness with beauty and success. A recent study examined influences of sociocultural effects by studying the incidence of anorexia nervosa in Curaçao, a society undergoing

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TABLE 12.1. Comparison of important clinical features of anorexia nervosa and bulimia nervosa.

Important features for anorexia nervosa	Important features for bulimia nervosa
Significant weight loss below normal range or refusal to maintain normal weight for age and height[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]
Amenorrhea in women[a]	Menstrual irregularities

[a]Required for the diagnosis according to DSM-IV.
[b]A minority of bulimic patients are above the normal weight and some are below the normal weight range.
[c]In DSM-IV, anorexia nervosa is subtyped into binge eating/purging and restricting subtypes.
[d]In DSM-IV, denial of the seriousness of the low weight may substitute for this criterion. Adapted from reference (157).

a socioeconomic transition (5). The overall incidence of anorexia nervosa was much lower than in the United States or in the Netherlands, and the authors found that sociocultural differences within the island were related to anorexia nervosa. The majority population on this island is black, and no cases of anorexia nervosa 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 anorexia nervosa had been more exposed to high-income western cultures. The incidence of anorexia nervosa among the white and mixed-race Curaçao 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 bulimia nervosa. Although early reports suggested a specific association between bulimia and a history of sexual abuse, because it does occur with some frequency in bulimic patients, this apparent association is not specific to bulimia nervosa, 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 bulimia nervosa (7). Other data suggest some differences in early experiences occurring in anorexia nervosa and bulimia nervosa. For example, critical comments by family regarding eating, weight, and shape have been found to be more prevalent in bulimic patients compared with anorectic patients (8).

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 percentage of women develop eating disorders. In addition, descriptions of anorexia nervosa go back to the 19th century, long before there was an emphasis on thinness.

1.2.1. Neuroendocrine Factors

Early neuroendocrine theories for anorexia nervosa were based on the observation that amenorrhea and disturbed hypothalamic thermoregulation are independent of emaciation in anorexia nervosa, and, thus, Russell (9) proposed that hypothalamic dysfunction contributes to the disorder. Neuroendocrine alterations in anorexia nervosa are common, and controversy regarding the pathogenesis of these changes continues (10–12). Many of these changes relate directly to weight loss. These include alterations in thyroid-stimulating hormone (TSH) response to thyrotropin-releasing hormone (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, because 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 seems 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.

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 anorexia nervosa and with bulimia nervosa do behave as if their satiety and control of eating mechanisms are deranged. Anorectic patients, compared with normal control subjects and with bulimic patients, endorse lower hunger ratings and higher fullness ratings in response to test meals (15). In contrast, bulimia nervosa patients eat significantly more food and rate their hunger afterwards as higher and their fullness as less than

non-eating disorder control subjects when provided meals in laboratory settings (16). An extensive body of animal research has shown that satiety is determined by postingestive events in the upper gastrointestinal tract, and a number of abnormalities relative to satiety and postingestive events have been found in bulimic 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. Postprandial release of cholecystokinin was found to be abnormally low in bulimia nervosa patients (17), whereas, in anorectic patients, some studies found elevations of basal levels of cholecystokinin (18). Other abnormalities relative to satiety in bulimic patients include enlarged gastric capacity (19), delayed gastric emptying (20), impaired gastric relaxation (21), and even abnormalities in functioning of the vagus nerve (22). Other neuropeptides, including beta-endorphin, neuropeptide Y, vasopressin, and leptin, have been investigated in anorexia nervosa and bulimia, with variable results (12). Although these abnormalities in anorectic patients 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 anorectic patients 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 (23, 24).

1.2.3. Neurotransmitter Changes

Barry and Klawans (25) proposed that increased dopaminergic activity may account for major signs and symptoms of anorexia nervosa, 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 anorectic patients (26, 27). Using positron emission tomography (PET) to assess dopamine D2/D3 receptor binding, a recent small controlled study of weight-recovered anorectic patients found increased receptor binding in the anteroventral striatum in the anorectic patients, and receptor binding in the dorsal caudate and dorsal putamen was positively correlated with harm avoidance (27). Although the data lends support to the possibility that dopamine changes could contribute to the characteristic harm avoidance or increased physical activity found in anorectic patients, much work still needs to be done to assess the role of dopamine in eating disorders.

Much attention has recently been given to the role of serotonin in the eating disorders. Anorectic patients and bulimic patients have been found to have alterations in 5-HT metabolism. Reduced basal levels of cerebrospinal fluid (CSF) 5-HIAA have been found during the acute low-weight phase of the illness in anorectic patients compared with control subjects, and because 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 (26, 28). However, levels of CSF 5-HIAA have been found to be elevated in long-term recovered anorectic patients (29), leading to the possibility that there may be a trait serotonin abnormality that predisposes to the possibility of anorexia nervosa. Because increased serotonin activity has been implicated in obsessive and anxious individuals, it is also possible that this altered serotonin activity in weight-recovered anorectic patients may contribute to their persistent symptoms of perfectionism, obsessiveness, and anxiety. It could be that, in anorectic patients, 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 bulimia nervosa, both during the acute symptomatic phase (30) and after symptom recovery (31), but because dieting itself can affect serotonin (32), 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 bulimia nervosa comes from the fact that in multiple placebo-controlled double-blind studies using serotonergic antidepressants to treat bulimia nervosa, there is a significant reduction in binge-eating and purging behavior, even in bulimic patients who are not depressed (33).

Using selective neurotransmitter radioligands with PET, studies confirm altered 5-HT neuronal pathway activity in anorexia nervosa. Compared with control subjects, recovered restricting anorectic patients have been found to have reduced 5HT2A activity in the amygdala and hippocampus, as well as in the cingulate, sensorimotor, and occipital/parietal cortical regions (34). Additionally, recovered anorectic patients have increased 5HT1A receptor activity in the presynaptic raphe nucleus and cortical–limbic–striatal postsynaptic receptors (34). Because 5HT1A postreceptor binding in many cortical areas was positively correlated with trait anxiety and with harm avoidance in the anorectic patients, these findings support the possibility that these alterations might contribute to increased anxiety, a common premorbid trait in anorectic patients, and, hence, also to vulnerability for the development of eating disorders.

1.2.4. Structural/Functional Brain Changes/Imaging Studies

Resting brain imaging studies have confirmed that low-weight anorectic patients have enlarged ventricles and widened sulci (35). Although these alterations seem to be at least partly reversible with weight restoration, some data suggests that changes may persist after recovery (36). Recent magnetic resonance imaging (MRI) technology has been used to study volumetric gray and white matter in anorectic patients (Fig. 12.1). Studies have found abnormalities of both gray and white matter in low-weight anorectic patients, and that these abnormalities may resolve to varying degrees over time

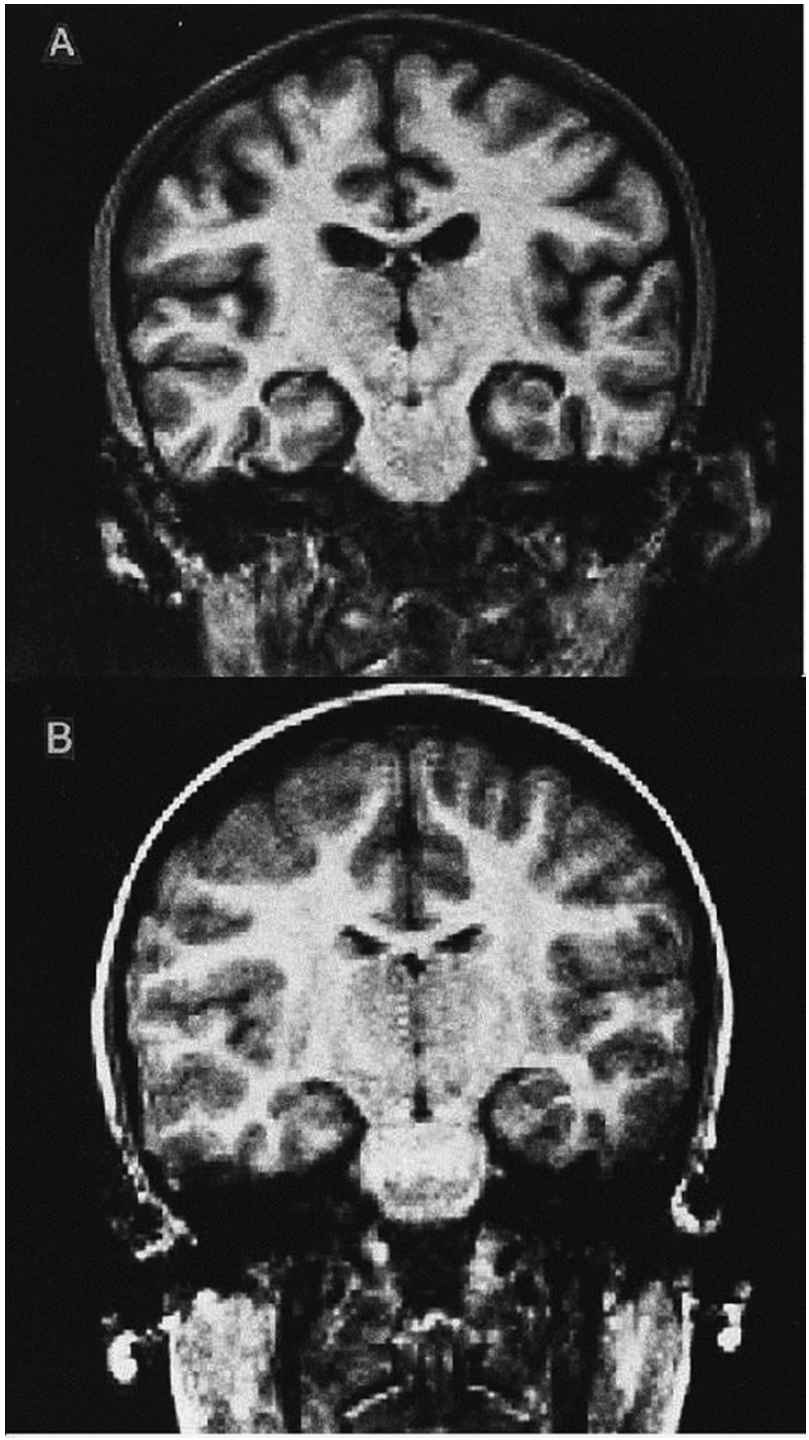

FIGURE 12.1. Coronal MRI scan of an 11-year-old patient with anorexia nervosa (**A**) compared with that of an 11-year-old healthy control subject (**B**). **A** Sulcal enlargement and marked dilation of the third and lateral ventricles. **B** Normal anatomy at the same level. Reprinted from reference (158), with permission from Elsevier.

(37–39). Most studies found no association between duration of illness and structural abnormalities. The meaning of these structural changes are unclear.

Single-photon emission computed tomography (SPECT) and PET studies in low-weight anorectic patients have consistently shown temporal hypoperfusion alterations; some patients have frontal, cingulate, or parietal changes; and there is some evidence of persistence of the temporal alterations after weight recovery (40–43).

Stimulus processing in anorectic patients has recently been studied using functional MRI (fMRI). Anorectic patients, compared with healthy control subjects, showed significantly more anxiety and a greater signal response in the left insula, anterior cingulate gyrus, and left amygdala–hippocampal region after viewing high-calorie foods compared with low-calorie foods (44). The result was interpreted as activation of the limbic and paralimbic fear network. Another fMRI study challenged anorectic patients and healthy control subjects with computer-based images of themselves distorted to various specified body mass index (BMI) levels (45). After viewing the heavier images of themselves, anorectic patients exhibited greater relative activation of the right amygdala and right fusiform gyrus. This was again interpreted as activation of the fear network.

Results of the structural and functional neuroimaging studies to date indicate that anorectic patients do have alterations in brain structure and brain metabolism particularly when they are at low weight. Although the causes of these changes are unknown, starvation seems to play a significant role. In addition, several studies suggest alterations in stimulus processing.

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, although there is uncertainty regarding the size of the genetic versus environmental contributions, both for anorexia nervosa and bulimia nervosa. Increased rates of eating disorders among female family members of anorectic patients have been reported in several large series (46–48). For example, Theander (46) found a morbidity risk of anorexia nervosa among sisters of anorectic probands to be 6.6%. There is evidence of cross-transmission between the eating disorders, suggesting a shared familial liability (49). Klump et al. (50) found the lifetime risk of anorexia nervosa or bulimia nervosa among female relatives of an individual with an eating disorder to be 7 to 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 (OCD). However, the vulnerabilities for depression and anxiety seem to be transmitted independently of the vulnerability for eating disorders, whereas obsessive–compulsive personality traits, such as the vulnerability for eating disorders, seem to be a shared familial vulnerability (48).

Twin studies help to clarify the contribution of genetics to the familiality of eating disorders. Clinic-based samples indicate that the concordance rate for anorexia nervosa is approximately 55% in MZ twins and 5% in DZ twins, whereas, for bulimia nervosa it is 35% in MZ twins and 30% in DZ twins (49). Although this suggests a significant heritability for anorexia nervosa but not for bulimia nervosa, population-based studies have also shown a significant heritability for bulimia nervosa (51, 52). Although it is estimated that greater than 50% of the variance in the occurrence of anorexia nervosa can be accounted for by genetic factors, twin studies suggest that 17 to 46% of the variance in both anorexia nervosa and bulimia nervosa is accounted for by nonshared environmental factors (53). 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 (53). More data are available for bulimia than for anorexia nervosa.

Molecular genetic studies are being done to identify underlying genes and loci. The focus has been on polymorphisms in the serotonin-related genes, because the serotonin neurotransmitter system has been shown to be important in mood and eating regulation. To date, no studies, including a large multicenter family-based study, has been able to confirm any associations with eating disorders (54).

2. Comorbidity

It has been hypothesized that eating disorders represent atypical affective disorders occurring in adolescent girls at a time in their lives when body image issues are important. Some findings support this view. Major depression, with approximately 45 to 68% meeting diagnostic criteria, is the most common comorbid disorder in both anorexia nervosa and bulimia nervosa (55–58). There is some evidence that women with the bulimic subtype of anorexia nervosa have more affective disorders than those with the restricting subtype of anorexia (59). Symptoms of depression often predate the onset of the eating disorder, and follow-up of anorectic patients suggests an increased risk for affective disorder (58, 60). Controlled family studies have shown an increased incidence of primary affective disorder in the families of anorectic patients compared with families of control subjects (47, 58, 61). 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 TSH response to TRH, also are found in anorectic patients, although the abnormalities seem to be reversible with weight gain (62–66). Semistarvation can certainly contribute to depression (67), and there is evidence that starvation can lead to elevations in corticotropin-releasing hormone (CRH), which can contribute to depression (68).

A relationship between bipolar (primarily subthreshold) disorder and eating disorders, primarily bulimia, has been suggested. Six studies evaluated bipolar disorder in the relatives of eating disorder probands. Two studies found significantly higher rates of bipolar disorder in the relatives of anorectic patients than control subjects, and one study found higher rates of bipolar in relatives of bulimic patients than control subjects. Three controlled family interview studies have found depressive disorders, but not bipolar disorders,

in the relatives of eating disorder probands. To our knowledge, no controlled studies have evaluated eating disorders in the relatives of bipolar probands. This issue deserves further attention, because phenomenologically, eating dysregulation, mood dysregulation, impulsivity and compulsivity, and exercise and activity, show some commonality between bipolar and eating disorders (69).

Newer evidence suggests that both anorexia nervosa and bulimia nervosa are related to anxiety disorders, including OCD, and that anxiety is central in both the etiology and maintenance of eating disorders. During the acute illness, anorectic patients suffer from obsessions regarding 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 (67), and caloric deprivation may create an environment that allows the exacerbation of obsessional tendencies. A 10-year follow-up study indicated that 65% of anorectic patients had lifetime diagnosis of an anxiety disorder, with 34% having social phobia, 15% with agoraphobia, and 26% with OCD, even excluding obsessions and compulsions regarding the eating disorder symptoms (58). In bulimia nervosa patients, although one study resulted in a lifetime diagnosis of OCD in 32% of patients (70), other studies find a lower rate of OCD in bulimia nervosa patients compared with anorectic patients (71). In one recent study, two thirds of both types of eating disorders had one or more lifetime anxiety disorder diagnosis, with OCD occurring in 41% and social phobia in 20% of patients. 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. In addition, subjects who had a history of eating disorder but were not currently ill with it still showed evidence for high anxiety (72). Recent imaging studies indicate that, in anorectic patients compared with control subjects, there is evidence of greater activation of the limbic and paralimbic fear network when confronted with food and body image stimuli (44, 45).

The relationship between eating disorders and substance abuse has received considerable attention. The available data supports a relationship between the bulimic behaviors of binge eating and purging and substance abuse, whether this is in an individual with bulimia nervosa or in the binge/purge subtype of anorexia nervosa (73). Substance abuse is not common in the restricter subtype of anorexia nervosa. Roughly 22% of bulimia nervosa patients report high alcohol intake, and 28% report a history of other drug abuse (74). There is also a high frequency of eating disorders in women who present for treatment of substance abuse. In a study of 61 adolescent girls with a substance abuse problem, 28% had a diagnosable eating disorder (75). One possible reason for the association of eating disorders and substance abuse is that food deprivation increases the likelihood of substance abuse (76). However, this does not explain why there is so little substance abuse in restricter anorexics, who show even more food deprivation than the bulimia nervosa patients, and why there is more substance abuse in the binge/purge anorectic subtype than the restricter anorexic 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 (77).

A "multi-impulsive" syndrome has been described in some patients with bulimia nervosa (74), 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 bulimia nervosa and Axis II disorders, particularly Cluster B or BPD (78, 79). In the study by Herzog et al., 27% of an outpatient sample of 210 girls and women with eating disorders were diagnosed with personality disorders, and the most common personality disorder was BPD (9%); none of the restricting anorexic patients had this diagnosis, but 8% of the bulimia nervosa patients and 12% of patients with the binge/purge subtype of anorexia nervosa 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 anorexia nervosa. In one study of eating disorder patients, 35% of those with restricting anorexia nervosa met criteria for obsessive–compulsive personality disorder (OCPD), compared with 5% of those with bulimia nervosa (71); and, in another study of adolescent girls, those with anorexia nervosa had higher rates of OCPD compared with the normal control subjects (80). Cluster C changes may, in part, be related to starvation. Changes consistent with OCPD have been described in men undergoing semistarvation, without these characteristics being present before the semistarvation period (67). However, in a 6-year follow-up study of patients with a history of anorexia nervosa who no longer met diagnostic criteria for anorexia nervosa and who no longer were malnourished, Cluster C personality traits were still present compared with a control group (81).

3. Epidemiology

Anorexia nervosa historically has seemed an uncommon illness. In 1973, three separate psychiatric case registers in Scotland, England, and the northeastern United States supported a low annual incidence of approximately 1 case per 100,000 people (82). Evidence suggests that the incidence of anorexia nervosa has increased. One study indicates that the incidence nearly doubled from 1960 to 1976 (83). Another study, which identified all anorectic patients in one Midwestern community between 1935 and 1984, indicated that the incidence has increased among girls and women 15 to

24 years of age but not among older women or among men. The overall age-adjusted incidence rate per 100,000 person-years was 14.6 for girls and women (84).

Recent prevalence studies indicate anorexia nervosa to be a common disorder in the age group at risk: 12 to 30 years. In 1976, Crisp et al. surveyed nine populations of high school girls in England. The prevalence was 1 severe case in 200 girls, and in those age 16 years or older, the prevalence was even higher—1 severe case in every 100 girls. In the Midwestern community study described in the previous paragraph, the prevalence also was 1 case per 200 girls and women 15 to 19 years of age. Crisp et al. (85) and other authors have reported anorexia nervosa to be more prevalent in the higher socioeconomic classes, but no controlled studies support this hypothesis.

Anorexia nervosa occurs predominantly in girls and women. Only 4 to 10% of cases occur in men (84, 86). Clinically, except for amenorrhea, male anorectic patients are remarkably similar to the female patients. Anorexia nervosa seems to be uncommon in poorly developed countries, and it is infrequent among blacks in the United States. It is overrepresented in women in certain occupations, such as models and ballerinas, who must rigorously control their body shape (4, 13).

Bulimia nervosa is more common than anorexia nervosa, with the lifetime prevalence estimated to be 1 to 3% of women in the United States. Most research studies of prevalence have been performed in college and high school girls, but it is unclear what the prevalence rate is in the general population. As with anorexia nervosa, bulimia nervosa occurs predominantly in women, with only approximately 10% of cases occuring in men. Bulimia nervosa typically develops a bit later than anorexia nervosa, in later adolescence or early adulthood. Similar to anorexia nervosa, bulimia nervosa is more common in western cultures, where food is abundant and slimness is highly valued. There is evidence that bulimia nervosa rates increased and are more prevalent in those who were born after 1960 (87). Dieting typically precedes the onset of bulimic symptoms, although there are cases where binge eating precedes dieting (88).

4. Clinical Picture

4.1. Anorexia Nervosa

The essential clinical features of anorexia nervosa and a comparison with the features of bulimia nervosa are listed in Table 12.1. Anorexia nervosa typically begins with a simple diet adopted in response to concern regarding 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 patient'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 anorectic patients overestimate the width of body parts, but there are wide individual variations among anorectic patients in their body size estimates (89, 90). Compared with anorectic patients 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 (89, 91). Although body size overestimation is significant in a subgroup of anorexia nervosa patients it cannot be considered unique to this population, because some studies have found no significant mean differences between anorectic patients and control groups (89, 91).

Anorectic patients 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 regarding these behaviors is often met with denial. Yet anorectic patients 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 (92,93). They also may become hyperactive and engage in strenuous ritualistic exercises to control weight.

Attempts to delineate subgroups have focused on clinical differences between anorectic patients who binge eat and those who do not. In two large surveys, bulimic anorectic patients were characterized by self-induced vomiting and by abuse of laxatives and diuretics (92, 93). 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 anorectic patients who exclusively dieted to lose weight. In one study, a high frequency of obesity was found in mothers of the bulimic anorectic patients (93). The delineation of these subgroups extends to the families. The incidence of alcoholism and drug abuse disorders is higher in families of bulimic anorectic patients than in families of nonbulimic anorectic patients (94, 95). The bulimic subgroup of anorexia nervosa remarkably shares characteristics with bulimia nervosa. 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.

4.2. Bulimia Nervosa

The main feature that distinguishes bulimia nervosa from anorexia nervosa 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, bulimic patients 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 (96). Bulimic patients can usually identify safe foods that do not result in a binge, and unsafe or "forbidden" foods that result in a binge (usually high-calorie carbohydrate or fat foods). This was demonstrated in a study that found that bulimic patients 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 (97). 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 bulimic patients at first feel they can control their eating binges, over time, there is an increase in binge frequency and duration. A small subgroup does not purge. Body weight in bulimic patients is typically in the normal weight range.

As in anorexia nervosa, 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 (74).

5. Clinical Course

5.1. Anorexia Nervosa

Onset of anorexia nervosa occurs from prepuberty to young adulthood, generally between the ages 10 and 30 years. Most commonly, the disorder begins between the ages of 13 and 20 years, and the mean age onset is age 16 years (46, 98). Although rare cases outside this range are described, they must be scrutinized to exclude other psychiatric or organic disorders simulating anorexia nervosa. 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.

Anorexia nervosa 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 anorectic patients 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 (46, 60, 99–102). Reviews of studies with similar longer-term follow-up periods indicate the following (103, 104). Overall, approximately 50% of patients fully recover over time; approximately 30% do fairly well but continue to have significant eating disorder symptoms as well as problems with social, sexual, and psychological adjustment; and approximately 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% of patients. Obesity develops in less than 8% of patients. Although weight may be normal at follow-up, abnormal eating behavior may persist; one half of patients still practice dietary restriction and avoid high-calorie foods, and binge eating or compulsive overeating, vomiting, and laxative abuse are common; and many patients meet the criteria for bulimia nervosa at follow-up. Thus, there is a fair amount of crossover from anorexia nervosa to bulimia nervosa. Up to half of anorectic patients have unipolar affective disorder at follow-up (58, 60). 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 anorectic patients who, at follow-up, have low weight and abnormal eating behavior or are preoccupied with food and weight (58).

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 (46, 105). 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 predictor of relapse (106).

The anorectic illness carries a considerable mortality, with a standardized mortality ratio up to 12.82 (101). 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 studies report a rate greater than 15%. Longer-term studies tend to show higher mortality rates (105, 107–109). The most notable of these, a Scandinavian study conducted during 22 years, found an 18% mortality (109). The suicide rate was 5%. Most studies report suicide rates of approximately 1%. One recent prospective study of 246 women with eating disorders followed over 11 years found no deaths from bulimia nervosa, whereas the standardized mortality ratios both from death and from suicide were significantly elevated in anorexia nervosa patients (110). All deaths in this study were in anorectic patients with a

history of binge–purge behavior, longer duration of illness, and with comorbid Axis I affective or substance abuse disorders. Some evidence of a decreasing mortality rate during the last 20 years is emerging, likely because of the establishment of specialized care units (111).

5.2. Bulimia Nervosa

The mean age of onset of bulimia nervosa is a bit later than anorexia nervosa, with mean age of onset of binge eating of 18 years (112). The onset of vomiting is, on average, 1 year later. Premorbid characteristics are similar to those for anorexia nervosa, except, unlike the restricter anorectic patients, in many patients there are generalized impulse-control problems. The typical bulimic patient is symptomatic for 3 to 6 years before seeking treatment, and the frequency of the bulimic behaviors generally increases with time (112).

Less is known regarding the course of bulimia nervosa than regarding anorexia nervosa, but it is clear that bulimia nervosa 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 (113). There is very little crossover to anorexia nervosa, and the mortality is much lower than in anorexia nervosa, on average 0.3% (113). Most of the follow-up studies of treatment studies indicate that approximately 50% are recovered at a follow-up interval of 5 years or more, whereas 20% continue to meet full criteria for bulimia nervosa, and 30% had experienced relapse into bulimic symptoms. One recent review of the follow-up studies for bulimia (114) indicates that there is no stable recovery for the first 5 to 6 years after intake into a bulimia nervosa study, but there is a general tendency for increase of recovery with increasing length of follow-up, so that after approximately 10 years, approximately 70% of patients show at least partial recovery. However, as many as 25% of patients may still have bulimic symptoms, indicating a high rate of chronicity.

Several prognostic indicators for bulimia nervosa have been identified (114). There is general agreement that a high degree of severity of bulimic symptoms, particularly vomiting, predicts a worse outcome, whereas a short duration of illness predicts a better outcome. Substance abuse seems to predict a worse outcome. BPD and Cluster B personality disorders predict a worse outcome, perhaps related to the issue of multi-impulsivity, which is present in many bulimic patients and which also predicts a worse outcome.

6. Medical Findings

Medical abnormalities and complications noted in anorexia nervosa and a comparison with those noted in bulimia nervosa are given in Table 12.2. Physical and medical abnormalities in anorexia nervosa 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 (115). Prolonged amenorrhea with low weight is associated with potentially irreversible osteopenia and an increased rate of pathologic fractures (116). 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 (117). 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 anorectic patients at low weight of an “immaturity” in the pattern of LH functioning, resembling that of prepubertal girls. After weight gain, the LH pattern usually returns to normal, but some anorectic patients 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 (118). Some other abnormalities are not clearly resolved with weight gain. For example, abnormal CT scan results of the brain may be found in more than half of anorectic patients (119), and there is evidence lacking that this always resolves with weight gain. Common physical findings in anorexia nervosa are hypotension, hypothermia, bradycardia, dry skin, and lanugo. Less common features are hair loss, petechiae, peripheral edema, and carotenemic skin.

Bulimia nervosa patients are less medically compromised (120, 121). Their most common problem is fluid and electrolyte abnormalities, which are found in approximately 50% of patients, secondary to variable combinations of vomiting, and 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 bulimic subtype of anorexia nervosa. Bulimic patients may be intermittently amenorrheic. Bulimic patients often have salivary gland swelling, typically of the parotid glands. The etiology of this is somewhat unclear, but likely related to vomiting, and mildly elevated salivary amylase changes are likely associated. Bulimic 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 because of vomiting (122). Rare but dangerous complications include gastric rupture or esophageal tear.

7. Differential Diagnosis

The major confounding diagnosis is bulimia nervosa. The unclear boundaries between anorexia nervosa and bulimia nervosa 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 bulimia nervosa and anorexia nervosa, bulimic patients generally

TABLE 12.2. Major medical abnormalities of anorexia nervosa and bulimia nervosa.

	Anorexia nervosa	Bulimia nervosa
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 tests	Elevated amylase
	Superior mesenteric artery syndrome	Pancreatitis
	Pancreatitis	
Cardiovascular	ECG abnormalities: arrhythmias, QT prolongation, bradycardia	Cardiomyopathy in ipecac abusers
		Hypokalemic-related ST changes, QT prolongation in ECG
	Altered circulatory dynamics	
	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
CNS	Nonspecific EEG abnormalities	Nonspecific EEG abnormalities
	CT/MRI:	CT/fMRI: decreased cerebral blood flow
	Enlarged ventricles	
	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 T_3, high rT_3 levels	Impaired TRH responsiveness
	Impaired TRH responsiveness	
Growth hormone	Elevated basal growth hormone level	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	

ESR, erythrocyte sedimentation rate; BUN, blood urea nitrogen; GFR, glomerular filtration rate; ECG, electrocardiogram; CNS, central nervous system; EEG, electroencephalogram; FSH, follicle-stimulating hormone; LHRH, luteinizing hormone-releasing hormone.

maintain weight within a normal range and do not show extreme pursuit of thinness. Body image disturbance has not yet been systematically assessed in bulimic patients. Amenorrhea is a variable feature of bulimia nervosa. Currently, amenorrhea is still required for the diagnosis of anorexia nervosa in women. However, there are patients who meet all of the criteria for anorexia nervosa except that they continue to menstruate (123).

Anorexia nervosa must be differentiated from the peculiar eating behaviors and weight loss that can occur in several

other disorders. In general, the differentiation can readily be made on the basis of positive criteria of anorexia nervosa, 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 anorexia nervosa. Whereas depressed patients are aware of a loss of appetite, anorectic patients generally have a normal appetite, which they may deny. Anorectic patients, in contrast to depressive patients, 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 sometimes seen in schizophrenic patients, usually on the basis of delusions. However, the delusions of schizophrenic patients 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 anorexia nervosa. 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 anorexia nervosa and bulimia nervosa. One important study, the Minnesota Semi-starvation Experiment (67), demonstrated that similar to patients with eating disorders, the healthy male conscientious objectors who were subjected to semistarvation quickly developed an intense preoccupation with food and eating, mood changes, diminished social interest, and, after several weeks, even a tendency toward binge eating. However, in general, starvation, resulting from causes other than anorexia nervosa, is associated with inactivity and apathy and not with the intense fear of weight gain, body image distortion, alertness, and hyperactivity, as seen in anorectic patients (124). 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 semistarvation (125).

The differential diagnosis of bulimia nervosa includes a variety of organic syndromes that 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.

Bulimia nervosa must be differentiated from binge-eating disorder, which is classified in DSM-IV under Eating Disorder Not Otherwise Specified (a category for individuals with clinically significant disturbances in eating behavior who do not meet criteria for any specific eating disorder). These patients have the episodic pattern of binge eating similar to the bulimic patients, but they do not show the inappropriate compensatory behavior characteristic of bulimic patients (e.g., purging, fasting, excess exercise). In addition, individuals with binge-eating disorder are almost all overweight, in contrast to bulimic patients, who are generally in the normal weight range.

8. Treatment

8.1. Anorexia Nervosa

Anorexia nervosa remains a serious disorder remarkably resistant to a wide range of interventions. To date, no psychological or pharmacological intervention has been identified that dramatically and reliably alters the dysfunctional thinking and associated behaviors that accompany it, and overall few controlled treatment trials have examined the treatments for anorexia nervosa. Because 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 regarding the best treatment. Treatment currently involves a combination of medical management, nutritional education, and rehabilitation, often using behavioral techniques, reeducative 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 (126, 127). 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 dilation 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 (128). However, a randomized controlled treatment study did not demonstrate a clear advantage, expressed as weight gain, for behavior therapy (129). 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 regarding 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 that first addresses the specific eating issues, followed

by psychological issues, is helpful for adolescents with anorexia nervosa who still reside at home (130–132).

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 (CBT), cognitive psychoanalytic and educational behavioral therapy, dietary counseling, individual supportive therapy, and family therapy (133–138). Although CBT has shown to have some effectiveness (138), interpersonal psychotherapy has also received attention (139). A recent controlled outpatient study comparing cognitive behavioral, interpersonal psychotherapy, 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, whereas CBT and interpersonal therapies did not differ significantly from each other (140).

There is, to date, no proven pharmacological treatment for anorexia nervosa. A major problem may be because of the neurochemical effects of starvation. Although a variety of medications, including antidepressants, antipsychotics, lithium, and antihistamines, have been studied in the treatment of low-weight anorectic patients, primarily focusing on their ability to promote weight gain and improve symptoms, no drug has proven to be of clinical value (141–146). Another approach is to use medications after weight recovery and evaluate their effectiveness on weight maintenance and improvements in comorbid psychopathology. One placebo-controlled study indicated that fluoxetine benefited nonbulimic weight-recovered anorectic patients in prevention of relapse after 1 year (147). However, a recent well-designed, randomized, double-blind placebo-controlled study of fluoxetine in weight-recovered anorectic patients treated for 1 year failed to demonstrate a benefit from fluoxetine in the prevention of relapse, although there was a significant benefit in reduction of anxiety in the fluoxetine-treated group (148). All patients in this study received CBT. There was no difference in results in the restricter versus bulimic subgroups.

Despite the generally negative results in controlled studies, most clinicians use 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 selective serotonin reuptake inhibitors (SSRIs) to treat depression and obsessive–compulsive symptoms, but low-dose novel antipsychotics are also used, as well as antianxiety agents. More double-blind studies of the antipsychotics as well and antidepressants are sorely needed.

8.2. Bulimia Nervosa

In contrast to anorectic patients**,** most bulimic patients 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 (149, 150). Many antidepressants have been demonstrated to be effective in significantly reducing the bulimic symptoms in the short term, and there is a definite antibinge effect separate from the effect on mood (33, 144). Fluoxetine is the only medication that has been approved by the US Food and Drug Administration in the treatment of bulimia nervosa, 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 (151). The difficulty is that the positive effect of the antidepressants is not sustained, and that relapses occur despite continued treatment with medications (144).

A novel pharmacological approach to the treatment of bulimia, targeting the peripheral nervous system, was recently reported by Faris et al. (22). 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 severely bulimic patients, 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.

CBT, either in a group setting or individual format, which focuses on restructuring the maladaptive behaviors plus the associated thinking that supports and maintains the disorder, has been repeatedly shown to be the most effective treatment for bulimia, even when compared with antidepressants (152–154). Results indicate that approximately one half of patients recover during the usual 4 to 6 months of treatment. Recently, another short-term therapy, interpersonal psychotherapy, has been studied and found to be comparable in efficacy to CBT for bulimia, except that it seems to take longer to get similar results (155). Studies have also been done investigating the combination of psychotherapy, usually CBT, and antidepressants (152–154, 156). In general, CBT is more effective than antidepressants, and the combination of antidepressants and CBT is more effective than antidepressants alone. Although bulimic symptoms do not seem to be improved with the combination of antidepressants and CBT over CBT alone, there is evidence that depression, anxiety, and possibly dietary restriction improves with the combination (153).

Although the treatment of choice for bulimia nervosa is CBT, many clinicians begin with an SSRI, such as fluoxetine or sertraline, because CBT 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

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Abstract This 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, seem 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. Although considered diagnostically reliable, ASPD and psychopathy are highly comorbid with substance dependence and narcissistic personality disorder because of similar criteria, making differential diagnosis difficult. Finally, treatment for psychopathy and ASPD is a very controversial subject; although meta-analytic findings demonstrate positive results, considerable evidence also indicates that these disorders are resistant to typical interventions.

Keywords Antisocial · Dimensional models · Pathology · Personality disorders · Psychopathy

1. Definition

The *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV) (1) defines antisocial personality disorder (ASPD) as a pervasive pattern of disregard for and violation of the rights of others. The primary diagnostic criteria of 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 (2, 3). In fact, the text of the DSM-IV indicates that psychopathy is another term for the disorder (1). However, some have argued that the constructs of ASPD and psychopathy are not interchangeable because of the failure of DSM ASPD to include the breadth of Cleckley's psychopathy traits (4, 5). In support, the most widely recognized psychopathy measure, the Psychopathy Checklist—Revised (PCL-R) (6), 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"' (2; p.206), which some suggest is a fundamental trait of psychopathy (7).

It is also helpful to understand ASPD from the perspective of general personality structure; more specifically, a maladaptive variant of personality traits evident within the general population. Our preference is to use the five-factor model of personality (FFM). As assessed via the NEO Personality Inventory—Revised (NEO PI-R) (8), the FFM includes five broad domains, each with six specific facets, as descriptors of basic personality. The domains include neuroticism (N: anxiousness, angry hostility, trait depression, self-consciousness, impulsiveness, vulnerability), extraversion (E: warmth, gregariousness, assertiveness, activity, excitement seeking, positive emotions), openness to experience (O: fantasy, aesthetic, feelings, actions, ideas, values), agreeableness (A: trust, straightforwardness, altruism, compliance, modesty, tender mindedness), and conscientiousness (C: competence, order, dutifulness, achievement striving, self-discipline, deliberation). Considerable research has been conducted using the FFM to understand psychopathy (9–11) and ASPD (12–14). Importantly, the FFM conceptualization articulates the similarities and differences between the psychopathy and ASPD constructs within a common framework. For instance, although both ASPD and psychopathy

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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); although psychopathy is also represented by high competence (efficient). 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 (unrealistic), and low vulnerability (fearless); whereas ASPD is represented by high vulnerability and depressiveness. In terms of E, both psychopathy and ASPD are represented by high excitement seeking (foolhardy), and high assertiveness (dominant), but the psychopathic patient is also low in warmth (cold and distant).

Thus, although ASPD and psychopathy seem to have substantial overlap, the pronounced differences regarding 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, between the two conceptualizations, considerably more research has been conducted for psychopathy, particularly within the pathology domain. Again, although we do not want to use the disorders interchangeably, the weight of the psychopathy literature deserves consideration.

2. Etiology

The results of twin and adoption studies indicate a strong genetic component for antisocial behavior. Generally speaking, genetic factors are thought 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 (15, 16). However, when additive (interactive) and nonadditive (singular) genetic contributions are assessed, the genetic contribution remains resilient. Waldman and Rhee (17) 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, 0.32) and nonadditive genetic factors (effect size, 0.09). The heritability of antisocial behavior is also supported by animal studies of temperament. Selection studies (in which 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 (18,19). These results indicate that specific, heritable genes may be important contributors to antisocial behavior.

Although no genes have been clearly identified as etiological precursors to ASPD and psychopathy, several candidates are being considered, including those that are thought to underlie the related predisposing disorder of attention-deficit hyperactivity disorder (ADHD), and those that are related to neurotransmitter systems relevant to aggressive and criminal behavior, such as the dopaminergic and serotonergic systems (17, 20, 21). In a review of this area, Minzenberg and Siever provided several genetic polymorphisms that are the focus of recent research in antisocial and aggressive behavior (20). Within the serotonergic system, alleles that are involved in the synthesis (*U* and *LL*), transportation (*s*), reception (5HT1B), and metabolism (*MAO-A*) of neuronal serotonin have all been associated with anger, aggressive behavior, and impulsivity, as have several receptor polymorphisms (*DRD2*, *DRD3*, *DRD4*) of the dopaminergic system, and catechol-O-methyltransferase (*COMT*), a polymorphism associated with the breakdown of dopamine and norepinephrine (see reference (20) for a review). Again, although these genetic variations have been associated with several of the symptoms associated with ASPD and psychopathy, these preliminary findings are not yet considered conclusive evidence of any specific genetic contribution.

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 (16,22). This finding is remarkably robust even when compared with other psychiatric disorders with known environmental components, such as affective and substance use disorders (23), and indicates something distinct regarding 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 (24). 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 (25). 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 (26). Nonshared environmental influences are also substantial contributors. Factors specific to the individual seem to account for fully 30% of antisocial behavior variance (15). 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 regarding 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 et al. (27) found that the environmental etiological effect of physical maltreatment remained. Thus, independent of one another, genes and environment account for important variance in criminal and delinquent outcomes. However, because of the strong interaction between these components, the significance of either etiological course remains difficult to quantify.

3. Epidemiology

The prevalence of ASPD in the general population indicates strong sex differences, with higher incidence in men than in women. Using the Diagnostic Interview Schedule (DIS), the Epidemiologic Catchment Area (ECA) study estimated ASPD prevalence to be 4.5% in men and 0.8% in women (28). However, ASPD prevalence rates tend to be similar across race. For example, ECA estimates demonstrated little difference between African American and white races (2.3% versus 2.6%, respectively), suggesting that ASPD tends to present with equal incidence across race and ethnicity (28).

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 are primarily based 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 (4). Psychopathy prevalence rates in prisons tend to be significantly lower than those for ASPD, leading researchers to think that psychopathy must be very rare in the broader general population. However, these prevalence differences between ASPD and 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 ASPD criteria toward criminal and delinquent behavior inflates ASPD prevalence in prison settings because of the nature of a correctional population (30). 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 (31). It may be that the widely accepted incidence differences between ASPD and psychopathy would cease to exist (or even be reversed) in other populations in which the psychopathy traits of manipulation and glib charm are emphasized, such as the professions of law or politics (30).

Very few studies have exclusively focused on racial or sex differences in psychopathy prevalence. At this point, there is little evidence that psychopathy exists differentially across race (32, 33), although a handful of studies have reported a higher incidence in African Americans than whites or European Americans (34, 35). Sex differences in psychopathy prevalence are generally consistent with the ASPD findings (36), indicating that women are less psychopathic than men (37). Known sex differences in the facets of the FFM (38) may explain why. For example, Costa et al. (38) 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 extraversion domain, and the dutifulness facet of the conscientiousness domain. Additionally, women score lower than men on the excitement seeking and assertiveness facets of extraversion. In sum, the facets in which the psychopathic person is low (see Sect. 1 Definition) 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 extraversion domain; and the dutifulness facet of the conscientiousness domain). Likewise, the facets in which the psychopathic persons score high are facets in which men score higher than women (e.g., the excitement seeking and assertiveness facets of extraversion). 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 sex differences in psychopathy are to be expected.

4. Clinical Picture

According to the DSM-IV, a diagnosis of ASPD is contingent on 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 regarding 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 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 ASPD criterion set, specifically, glibness, arrogant self-appraisal, lack of empathy, and shallow affect. These indicators might suggest that the psychopathic person is more charming, self-assured, and cold-hearted than his ASPD counterpart, thereby making the psychopathic person 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 psychopathic person "appears almost as incapable of anxiety as of profound remorse," (2; p.340) and demonstrates "a relative immunity from such anxiety or worry as might be judged normal or appropriate" (2; p.206). Many experts in the psychopathy field continue to support Cleckley's assertion that the psychopathic person is low in anxiousness (10), although this criterion ultimately failed to appear in the PCL-R because of poor item-total correlations (39). In sharp contrast to psychopathy, ASPD is said to be associated with high levels of anxiety and other affective disorders (1). The DSM-IV states that individuals with ASPD "may also experience dysphoria, including complaints of tension, inability to tolerate boredom, and depressed mood" (1; p.702) and may be prone to both anxiety and depressive disorders (1). Although 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 (40, 41). 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, because it makes the assumption that criminal behavior, rather than personality features, is a primary symptom of the disorder (4, 32). 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" (31; p.79). Many studies have indicated that the ASPD criterion set correlates more highly with Factor 2 than with Factor 1 (e.g., (42, 43)), thereby supporting the heavy concentration of behaviors and the relative lack of personality characteristics in ASPD. However, although 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 (44, 45), 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. Because of this saturation of antisocial behavior, the PCL-R has received criticism comparable to the ASPD criterion set (46). To date, it remains unclear whether the PCL-R can be effectively applied within noncriminal settings, because the reliable assessment of antisocial activity becomes much more difficult in such populations.

Although criminal and irresponsible behaviors seem to be important to the construct of psychopathy, some maintain that antisocial behavior deserves no role in the diagnosis of psychopathy whatsoever because of its role as a consequence, rather than a symptom, of the disorder (47). These authors argue that although 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 (48). 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 (49). 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 (49), and "actually degraded the measurement of psychopathy" with their inclusion (46; 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" (46; p.99).

Work has begun to place 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 (50). Among these are the Psychopathic Personality Inventory (7) and the FFM conceptualization of psychopathy (10), both of which have demonstrated positive associations with criminal and delinquent behaviors (7, 10, 51), convergence with other psychopathy measures (52, 53), and predicted relations to other known correlates of psychopathy, including performance on laboratory tasks of aggression and deliberation (11). Thus, the assessment of psychopathy does not seem to be reliant on antisocial behavior, and it can be achieved through a personality-based measure.

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.

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 (54). This superego pathology is associated with an "incapacity to experience self-reflective sadness" that ultimately results in callous, tough-minded behavior (55). This classic picture of the psychopathic person was modified in later conceptualizations, and is reflected in Cleckley's and Hare's descriptions of "semantic dementia," in which abnormal affective processing is the prime feature of the psychopathic person's pathology (2,4). Hare has described the psychopathic person as being "without conscience," a deficit that ultimately results in ruthless, manipulative, cold-hearted, and violent behavior (56). This prevailing and longstanding conceptualization of psychopathic pathology has pervaded the research, and has recently been extended into laboratory task designs (57). Studies assessing the psychopathic person's autonomic reaction to emotional words and fearful images seem to be supportive of abnormally deficient affective processing, although the psychopathic person's cognitive reports of emotional responses have been found to be similar to those of nonpsychopathic people (4, 57).

5.2. Neuroanatomical Abnormalities

Structural and functional brain impairments have also been advanced as possible underlying pathologies of antisocial behavior (58, 59). Recent reviews of brain imaging studies of antisocial populations implicate abnormal functioning in the temporal cortex (60, 61), amygdala and hippocampus (62, 63), angular gyrus (64), and prefrontal cortex (64–66). In addition, negative correlations have been reported between PCL-R scores and prefrontal gray volume, indicating that psychopathic people have reduced prefrontal gray matter. The brain areas implicated seem to be consistent with the existing research on antisocial behavior and psychopathy. Prefrontal cortex functioning deficits have been independently associated with poor executive functioning and risky behavior, which are cardinal characteristics of psychopathy (67). In addition, the aberrant functioning of the amygdala in those with psychopathy may assist in understanding the psychopathic person's deficits in emotional processing and learning of stimulus-reinforcement associations (58). Although functional and anatomical deficits seem to be 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.

5.3. Psychophysiological Arousal System Impairments

Another influential theory of ASPD pathology comes from Gray's three-arousal model of the nervous system (68). 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 versus 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 (69, 70). 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 (71) 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 psychopathic person 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 with secondary or "neurotic" psychopathic people. Although low skin conductance is widely discussed in the literature, Raine's (72) 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 (72). Interestingly, although low skin conductance has been associated with crimes of evasion (e.g., white collar crimes and customs offenses) (73), it has not been found to be associated with other criminal activity, such as violent offenses (73). Additionally, although low skin conductance is associated with later institutionalization in behaviorally disordered children, it does not seem to be predictive of arrest (74).

Other autonomic arousal assessments have also been used to investigate psychophysiological functioning in the psychopath, including heart rate and startle response (75, 76). Low resting heart rate levels have been associated consistently with antisocial behavior in noninstitutionalized individuals, providing support for Gray's theory (72). However, studies of incarcerated populations generally fail to find group differences between psychopathic people and nonpsychopathic people, indicating that this finding may be a predisposing factor to antisocial behavior in general rather than psychopathy (72).

Startle response deficits are also associated with antisocial behavior. Patrick et al. (76) found that psychopathic people 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 (77–79).

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), because the psychopathic person typically seems to be intact in most of these areas (2, 80). In fact, recent evidence indicates that violence is positively correlated with intelligence scores in psychopathic adults (81), and psychopathy scores are positively related to verbal, analytic, creative, and practical abilities in children (82, 83). However, the psychopathic person'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 (84, 85).

Existing literature on the cognitive attributes associated with psychopathy indicates that the psychopathic person experiences stable deficits in the cognitive domains of attention (85, 86) and response modulation (87, 88). Laboratory task paradigms designed to assess the allocation of attention indicate that, despite intact perceptual and autonomic processes, the psychopathic person is unable to switch attention from an ongoing task to secondary (or peripheral) information when appropriate (86, 89, 90). 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" (88). Many researchers think that this may underlie the behavior control problems that characterize psychopathy (88). According to Newman, psychopathic people continue approach behaviors even if maladaptive, and are unlikely to consider contextual information that may be helpful in choosing alternate responses (87). Newman et al. (88) explored the inability of the psychopathic person to inhibit a dominant response to a card playing task of worsening odds and found that psychopathic people continued for more trials of unlikely success with a dominant response set in comparison with nonpsychopathic people. This effect has been replicated several times over, and continues to a productive area of research in the pathology of psychopathy (88, 91).

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 that are thought to underlie

the construct, such as aggressiveness, impulsivity, sensation-seeking, lack of empathy, and impairments in cognitive functioning (10, 92). Eysenck's theoretical framework placed personality between the physiological processes of arousal and antisocial behavior, implying that personality moderates the relation (93). 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 (71) proposed that the absence of anxious behaviors typically demonstrated by psychopathic people is caused by the psychopathic person's deficient emotional response to punishment or danger. In a description of this deficit, Lykken states that, for the psychopathic person, "the fear of punishment and the coercive voice of conscience both are, for some reason, weak or ineffectual" (93; p.134). According to Lykken, this absence of fear allows the psychopathic person to remain collected in high-stress situations, and inoculates them 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 (95). 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 (9). 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 seem 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. Although 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.

6. Clinical Course

Although ASPD and psychopathy are considered pervasive disorders, the specific antisocial behaviors associated with these diagnoses tend to remit with age (2, 96). 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 (2). Similar findings have been reported in the psychopathy research, albeit with slightly higher age estimates for remission of symptoms (96, 97). 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 years (98). Simply put, there seems to be a higher prevalence of ASPD and psychopathy in prisoners between the ages of 20 and 40 years than after age 40 years. 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 years, conviction rates drop but remain comparable for psychopathic and nonpsychopathic criminals (96, 98). Thus, although the reduction of criminal behaviors over time is significant for the psychopathic person, this "improvement" merely renders them comparable in criminality to their nonpsychopathic counterparts.

Interestingly, although the psychopathic person seems 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 (98) demonstrated that the psychopathy factors were differentially related to age; although 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 psychopathic person [including] egocentricity, manipulativeness, callousness, and lack of empathy" (pp. 604–605) was unrelated to age. In fact, Factor 1 scores of the 15- to 20-year-old age group were strikingly similar to Factor 1 scores of the 46- to 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 during the life course, the traits associated with psychopathy seem to continue to cause problems for the psychopathic person long after their 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 (99). Importantly, these domains are those thought to be most important to psychopathy, ASPD, and antisocial behavior in general (9, 11, 95). Thus, independently of the psychopathy and ASPD research, predictions regarding the course of these disorders are supported from the broad personality literature.

7. Differential Diagnosis

Differentiation between ASPD and psychopathy and other DSM-IV diagnoses can be problematic because many other disorders may present with overlapping symptoms. For instance, the ASPD criteria of irresponsibility, aggressiveness, and impulsivity may also be associated with DSM-IV Axis I 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 (2). 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 DSM-IV diagnoses. Despite this, two disorders continue to cause concerns in categorical diagnosis of ASPD. Substance use disorder and narcissistic personality disorder (NPD) remain difficult to distinguish from ASPD. Each will be discussed in turn.

Despite the relative reliability of the diagnostic criteria for ASPD, controversy remains regarding 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 (40). Additionally, PCL-R scores are strongly associated with substance use, particularly with Factor 2 of the PCL-R (100). However, the comorbidity estimates reported may be indicative of overlapping criterion sets (101); 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. Although suggestions have been made to incorporate exclusion criteria for DSM-IV ASPD in lieu of substance use disorder presence (102), 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 abuse exclusion criterion from being included in revisions of the DSM. On the other hand, both disorders seem to share a common underlying pathology and course (103, 104), 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 NPD (105, 106). In contrast to the criterion overlap with the irresponsibility and antisocial behaviors associated with substance use, NPD seems 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 (42); a pattern of correlations that is the mirror image for ASPD. Although the clinical and theoretical literatures of NPD and ASPD/psychopathy have grown independently, psychodynamic views generally incorporate narcissism into the psychopathy conceptualization (107, 108). 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 (109). However, because of concerns regarding diagnostic overlap and differentiation, the 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 (110).

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 will share diagnostic comorbidity with other DSM-IV personality disorders to the degree that they share overlapping constellations of personality traits (111). Lynam and Derefinko (112) 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 (112).

8. Treatment

There is considerable debate surrounding the efficacy of treatment for ASPD and psychopathy (113). Although some treatment-outcome research has indicated positive results for therapeutic interventions (114–117), other empirical evidence seems to suggest that the antisocial behaviors associated with ASPD and psychopathy are resistant to intervention, particularly for the psychopathic person (118–120). 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, high variability in results, and the clinical (versus statistical) meaningfulness of effect sizes (113, 117, 121). All of these factors contribute to the confusion regarding 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 psychopathic people benefit less from treatment than nonpsychopathic people, demonstrating higher attrition rates, lower clinical improvement,

higher violent recidivism, and more immediate recidivism after release than their nonpsychopathic counterparts (122–124). In addition, high PCL-R scores (particularly Factor 1 scores) have been associated with significantly higher recidivism rates in treated psychopathic people than untreated psychopathic people, suggesting that psychopathic people actually get worse with therapy (118, 119, 125). Thus, it is generally accepted that "nothing works" with respect to treating psychopathy (126); the psychopathic person seems to benefit less from treatment than nonpsychopathic people, and, in some cases, therapeutic interventions seem to increase future criminal activity in the psychopath, indicating that management, rather than treatment, may be the prescribed course for this type of offender (127).

This pessimism regarding treatment is enhanced by the overreliance on findings of a handful of landmark studies that report notably disappointing outcomes (128). 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 (118) reported that therapeutic community (TC) treatment significantly increased recidivism in psychopathic people compared with the untreated psychopathic group (77% versus 55%, respectively). However, the TC treatment used 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 (117; pp.285–288). Remarkably, the Penetanguishene study continues to be used as evidence that treatment of the psychopathic person is contraindicated. Perhaps even more surprisingly, although it seems apparent that therapeutic communities are not effective at reducing future criminal behavior (129, 130), they remain popular in prisons and psychiatric hospitals in Europe (113).

However, 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. Although pharmacological research suggests that specific symptoms of ASPD can be effectively reduced through medication (121, 131), concerns regarding 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, although 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 (132–134), the comorbidity between ASPD and substance abuse limits the use of this intervention beyond controlled settings because of its high potential for abuse when appropriate use of this medication cannot be monitored (121).

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 because of concerns regarding long-term treatment compliance (135, 136). Lithium has received considerable attention for use in those with ASPD because of its efficacy at reducing impulsive violent behaviors in nonbipolar adults and adolescents (137, 138). Additionally, selective serotonin reuptake inhibitors (SSRIs) such as sertraline and fluoxetine have been associated with significant reductions in overt hostility, aggression, and antisocial behavior (139, 140); as have anticonvulsants, including valproic acid (141), or its salt form, divalproex sodium (142, 143); and phenytoin (144). 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 (135, 136).

In addition, the manipulative and remorseless traits associated with psychopathy do not bolster optimism for therapeutic interventions. Some researchers think that despite good compliance with therapy and reported therapeutic improvement in correctional settings, the psychopathic person is simply using what he learns in therapy to enrich his criminal versatility and skill, thus accounting for negative outcomes (113). 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 ((119); see (113) for a review). Radical therapeutic change techniques aimed at modifying the character of the psychopathic person have been proposed, but, to date, they have limited empirical support (145). One example of this type of treatment is Cloninger's (121) 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 (121) 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. Although many agree that therapy targeting dysfunctional characteristics may be a very important aspect of the treatment of those with ASPD, it remains to be seen whether self-transcendence exercises are the most effective way of eliciting this type of change (146).

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 (117,121,128). 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 both adult offenders (117,147,148) and juvenile offenders (149, 150). In addition to overall effect

sizes, Lipsey (149) conducted moderator analyses on more than 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 seem to indicate something very different than the dismal conventional standard. When specific guidelines are followed, it seems as though significant gains can be attained (128, 150).

However, even though effect sizes indicate that treatment has a positive influence on recidivism, it is still questionable whether these are meaningful gains. Importantly, reported effect sizes in this area tend to gravitate toward a value of 0.20, which is comparable to that of a placebo effect (147–151). The clinical meaningfulness of this improvement may simply be insignificant. For instance, the treated offender may have committed rape fewer times in the 5 years after 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 (113). This type of study design has been found to overestimate treatment effects, thereby making these positive effect sizes even less convincing (150). Thus, although 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 effect.

In sum, clear conclusions regarding the efficacy of treatment for ASPD and psychopathy are difficult to draw. Although meta-analytic findings seem 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

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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 75,000 deaths per year and costs our society on the order of $150 billion per year. 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 10 to 15% in men and 5 to 10% in women. The etiology of alcoholism involves biopsychosocial components, with an estimated 50% of risk coming from genetics. Alcoholism and unhealthy alcohol use are underrecognized by clinicians although 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 alcoholic people. 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 Acamprosate · Alcohol abuse · Alcohol dependence · Brief intervention · Diagnosis · Genetics · Naltrexone · Treatment

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 (1; pp.39,40). The concept that a pathological use of alcohol is a disease was very 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 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* (DSM) since 1980 reflect changing opinions regarding 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,

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the criteria were revised in DSM-IIIR with greater emphasis on patterns of compulsive use and less emphasis on dependence and withdrawal. DSM-IV (2) 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 (for sake of clarity, examples related to alcohol are used).

A maladaptive pattern of alcohol use leading to clinically significant impairment or distress, as manifested by three (or more) of the following, occurring at any time in the same 12-month period:

1. *Tolerance, as defined by any of the following:*
   - *Need for markedly increased amounts of alcohol to achieve intoxication or desired effect*
   - *Markedly diminished effect with continued use of the same amount of alcohol*
2. *Withdrawal, as manifested by either of the following:*
   - *The characteristic withdrawal syndrome from alcohol*
   - *Alcohol is taken to relieve or avoid withdrawal symptoms*
3. *Alcohol is often taken in larger amounts or during a longer period than intended.*
4. *There is a persistent desire or unsuccessful efforts to cut down or control alcohol use*
5. *A great deal of time is spent in activities necessary to obtain alcohol (e.g., driving long distances), use alcohol, or recover from its effects*
6. *Important social, occupational, or recreational activities given up or reduced because of alcohol*
7. *Continued alcohol use despite knowledge of a persistent or recurrent physical or psychological problem(s) that is likely to have been caused or exacerbated by the use of alcohol (e.g., drinks despite family arguments about it, continued drinking despite recognition that an ulcer was made worse by alcohol)*

In addition to coding the diagnosis, the clinician is encouraged to specify whether physiological dependence is present or not as determined by criterion #1 or #2 above. Furthermore, the clinician can note course of illness specifiers, e.g., early partial remission, if so desired.

DSM-IV also provides criteria for Substance (Alcohol) Abuse. Alcohol Abuse does not involve the development of physical dependence or evidence of compulsive use patterns. Alcohol Abuse identifies individuals who have harmful use of alcohol without meeting diagnostic criteria for dependence. Individuals who have ever met criteria for alcohol dependence cannot be given the diagnosis of alcohol abuse under DSM-IV guidelines. The criteria for alcohol abuse are:

A maladaptive pattern of alcohol use leading to clinically significant impairment or distress, as manifested by one (or more) of the following, occurring within a 12 month period:

- Recurrent alcohol use resulting in failure to fulfill major role obligations at work, school, or home (e.g., repeated absences or poor work performance related to alcohol use; alcohol-related absences, suspensions, or expulsions from school; neglect of children or household)
- Recurrent alcohol use in situations in which it is physically hazardous (e.g., driving an automobile or operating a machine when impaired by alcohol)
- Recurrent alcohol-related legal problems (e.g., arrests for alcohol-related disorderly conduct)
- Continued alcohol use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of alcohol (e.g., arguments with spouse regarding consequences of intoxication, physical fights)

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 (3). 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.

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 toward 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.

2.1. Consumption

The United States is a drinking culture. Recent population studies indicate that 60 to 65% of the adult population report consuming alcohol in the past year (4). Average consumption, based on sales, for adults (ages 14 years and older) was 2.23 gallons of ethanol in 2004 (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 non-fortified wine, or 1.5 oz of liquor and, in the United States, to contain 12 to 14 g of ethanol. Studies in college students reveal an increasing trend in binge drinking. Weschler et al. (5) reported that 44% of college students reported binge drinking in the 2 weeks before completing a screening questionnaire (n = 14,138). More than 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 with samples questioned in 1993 and 1997. In the overall US population, survey studies indicate that approximately 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 (6). 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.

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, revealed that the 12-month prevalence rate of DSM-IV-defined alcohol dependence was 5.42% for men and 2.32% for women (7). Lifetime rates were 17.18% for men and 7.84% for women (8). Twelve-month prevalence rates were highest in the 18- to 29-year-old range and declined with increasing age. Twelve-month rates for abuse were 6.93% in men and 2.55% in women (7).

2.3. Morbidity and Mortality Attributable to Alcohol

Morbidity and mortality associated with alcohol is considerable. The Center for Disease Control reports that, in the United States, excess alcohol consumption contributes to 75,000 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 to develop deleterious consequences from alcohol consumption. It is incumbent on 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 (9). 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, because alcohol can be good for you, its risks are not that serious.

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 (see (10, 11)). Low-moderate levels of alcohol consumption in the 1 to 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, hemorrhagic stroke, and several types of malignancy, including breast cancer. Although some benefit for coronary heart disease remains evident at alcohol consumption levels of 3 to 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 (11). Women develop medical consequences from alcohol at lower total consumption levels than men, and their disease progression is faster than men (12).

Alcohol is involved in approximately 50% of fatal motor vehicle crashes, 17 to 53% of fatal falls, 37 to 64% of fatal burns, and 38% of fatal drownings (13–15). It is likely that alcohol's relationship to these traumatic deaths is significantly underreported.

2.3.2. Alcohol, Structural Brain Damage, Cognitive Impairment, and Dementia

A relationship between excessive alcohol consumption, cognitive impairment, and frank dementia have been noted for years. Whereas nutritional deficiencies, particularly thiamine deficiency, have been shown to be essential for some forms of alcohol 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 non-invasive

brain imaging techniques has led to a wealth of findings regarding brain changes in alcoholism (see (16) 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 the hippocampus, striatum, and thalamus, as shown in Fig. 14.1 (16). 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.

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 (17). 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 versus 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 (18) 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 score sleep problems, 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 (19). 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 (20). Sleep disturbances can normalize with sobriety, although this may take months (21).

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 (22). Differentiating alcohol-induced anxiety from primary anxiety disorders is challenging, and anxiety disorders should be carefully screened for in all alcoholic patients (23).

Suicide is a significant risk factor in alcoholism. One estimate is that up to 40% of alcoholic subjects will attempt suicide and 7% of alcoholic people will end their lives by suicide (24). 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 (24).

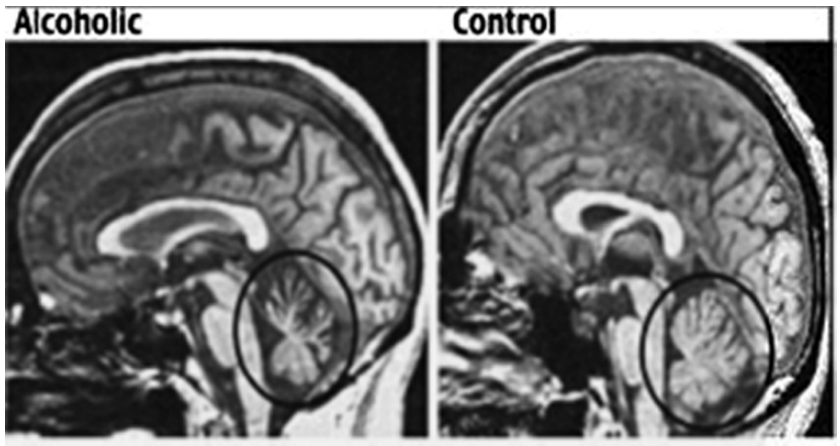

FIGURE 14.1. Midsagittal view of a magnetic resonance imaging (MRI) scan of the brain of an alcoholic person, showing severely shrunken folia of the anterior superior vermis compared with an age-matched control man (taken from reference (16); Fig. 2, p. 588; with kind permission of Springer Science and Business Media).

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) (25). 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 regarding the risks of drinking during pregnancy, the CDC estimates that 3% of pregnant women drink at levels associated with FASEs (26). 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.

3. Clinical Picture

The clinical presentation of alcohol-dependent patients is contingent on when in the course of the illness they present. There are no pathognomonic signs or symptoms of alcohol abuse or dependence. Although medical symptoms may bring an alcoholic person 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 alcoholic people than in nonalcoholic people. 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 person 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 person 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 (27).

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 (28–30).

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 (31). An estimated 5 to 24% of hypertension is associated with alcoholism (31); thus, internists should screen all hypertensive patients 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 (28), 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 amnestic syndrome) (32–36).

Uncommonly, myopathy may occur acutely with muscle pain and swelling or chronically with progressive weakness and atrophy. In addition, 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 (37) .

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.

4. Case History

JW, 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 regarding 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.

JW may or may not be an alcoholic person, but the pattern of his symptoms and his responses to questions regarding his drinking habits should raise his physician's index of suspicion.

5. Laboratory Findings

As is true of signs and symptoms, no pathognomonic laboratory measures 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 (38). 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-glutamyltransferase (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 to 70% range (39, 40). Its specificity is in the 75% range (i.e., in 25% of those with elevated GGT, the cause is not caused by alcoholism or heavy alcohol intake). GGT levels in alcoholic people returns to normal after approximately 4 to 5 weeks of abstinence, and it takes approximately 2 weeks of heavy drinking to acquire abnormal GGT levels (41).
- **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 to 75% of alcoholic inpatients (28, 42). A ratio of AST to ALT of greater than 2, with ALT values in the 2 to 8 times upper limit of normal range suggest alcoholic hepatitis (43).
- **Carbohydrate deficient transferrin (CDT)** is a relatively new blood test approved by the US Food and Drug Administration (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 to 5 standard drinks) for at least 2 to 3 weeks and persist for 1 to 2 weeks after sobriety. The advantage of CDT is its greater specificity compared with most other screening tests, e.g., specificity in the 90% range versus the 75% range for GGT. CDT has also been proposed as a tool to monitor treatment outcome because decreases in CDT support reports of sobriety and increases in CDT indicate possible relapse to heavy drinking (44).
- **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 to 95% of actively drinking alcoholic people, with most studies reporting 35 to 40%. An elevated MCV can also occur in folate and B12 deficiency, hypothyroidism, malignancies, and nonalcoholic liver disease, and these causes need to be excluded. The cause of the elevated MCV in alcoholic people is unknown, and it is more marked in alcoholic people who smoke. MCV returns to normal 2 to 4 months after alcohol ingestion ceases (45).
- **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 (28).
- **Combined GGT/CDT**: A variable derived from the combination of GGT and CDT, the gamma-CDT = $0.8 \times \ln(\text{GGT}) + 1.3 \times \ln(\text{CDT})$, has been shown to enhance discrimination of heavy alcohol use from social drinkers (46). A multinational World Health Organisation (WHO) study (47) 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.

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 (40). Clinicians will still need to be educated to use laboratory tests for these benefits to be realized.

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 (48) and the Alcohol Use Disorders Identification Test (AUDIT) (49). The CAGE is a four item questionnaire (See Table 14.1) and the AUDIT is a 10-item questionnaire; see Table 14.2 for complete scales. 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." For the U.S., this question should use 5 or more drinks for a man and 4 or more drinks for a woman. 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 (50). The AUDIT is better designed to detect heavy and hazardous drinking, whereas the CAGE is better at identifying alcohol abuse and dependence (50,51). Interestingly, the AUDIT-C and the third question of the AUDIT have shown results nearly comparable to the full AUDIT (52), 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 to identify patients in whom additional inquiries would be of value.

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.

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 (53), public hospital inpatients (54), private clinic outpatients (55), patients attending various units of a large university hospital or its affiliates (56), married or cohabiting residential treatment inpatients (57), college students (54), and untreated alcohol abusers (58). Despite the limitations of these studies, there are enough of studies to provide a reasonable idea of the various clinical courses that alcoholism can take.

Historically, the first modern attempt to delineate the course of alcoholism was undertaken by Jellinek (59). 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: 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 (3) 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 their early or middle 20s, its course was inexorable, with progression over 20 to 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 (60–65).

One of the first studies to challenge Jellinek's hypothesis of an inexorable progression of alcoholism was Lemere's 1953 study (66), 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

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 to 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

TABLE 14.2. (continued)

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.
A score of 8 or more is associated with harmful or hazardous drinking; and a score of 13 or more in women, and 15 or more in men, is likely to indicate alcohol dependence.

with alcohol problems becoming abstinent or reducing their drinking, represented the natural history of untreated alcoholism.

Vaillant (54) reviewed 10 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 alcohol using patients. These studies and others (56, 57), although methodologically disparate, are remarkably similar in indicating that approximately 2 to 6% of alcoholic people remit (are abstinent or drinking in a controlled fashion) each year. These approximations hold for samples of both treated alcoholic people (e.g., (54, 67–69)), "skid row" alcoholic people (70), and untreated alcoholic people (53, 57). Patients in successful remission are approximately two to three times more likely to be abstinent than drinking in a controlled fashion (54, 57), although one study, which followed socially stable patients, found the reverse (71). 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 (56, 72), although not all studies concur with this conclusion (71). These studies, therefore, partially support the hypothesis that alcoholism is, for some, a self-limiting disorder. However, as is pointed out in studies by Vaillant (54) and Pokorny et al. (73), the more numerous and more severe the symptoms of alcoholism, the closer the clinical picture is to Jellinek's stages and the more alcoholism seems 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 (74), 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 alcoholic people, 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 alcoholic people experience, which were noted earlier in this chapter and which frequently lead patients into outpatient or inpatient medical or psychiatric care, alcoholic people 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 (72).

The various morbidities and traumatic events associated with alcoholism lead to an average age of death of 55 to 60 years (34). Also of note is the finding of Vaillant (54) that offering intense, readily available treatment to alcoholic people does not lower their mortality rate, and the finding of Pell and D'Alonzo (75) that the mortality rate of recovered alcoholic people is not significantly different from that of alcoholic people who continue to drink. Although this latter finding has been supported (57), there are studies that indicate that survival is greater in those alcoholic people who are able to abstain or drink moderately than in those who continue as heavy and/or problem drinkers (76–78).

An overall view of the natural history of alcoholism reveals that an alcoholic person's first drink occurs at age 13 years, problem drinking begins between the ages of 18 and 25 years, first hospitalization for drinking problems occurs at approximately age 40 years, and death occurs between the ages of 55 and 60 years (34, 72, 79). This natural history differs somewhat for women, who begin problem drinking later than

men, and have a more rapid development of symptoms (12). 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 (34, 37, 80–86).

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 person spends much of their time sober (37, 87), with concomitant decreases at such times in alcohol-related problems. The disease seems to fit the pattern of a chronic relapsing illness, with periods of remission and exacerbation. Some alcoholic people seem to have permanent remissions either spontaneously, through internal resolve, or with the help of various factors in their environment (88). 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.

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 (17). It has been shown that 40 to 50% of hospitalized bipolar patients meet criteria for a comorbid alcohol use disorder (89). Other disorders with high rates of comorbid alcohol problems include antisocial personality, schizophrenia, generalized anxiety disorder, posttraumatic stress disorder, social phobia, attention deficit disorder, bulimia, and, to a lesser extent, unipolar depression (17).

Results from the National Epidemiologic Survey on Alcohol and Related Conditions revealed significant comorbidity between alcohol use disorders and drug use disorders (90). During 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 with 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.

9. Etiology

There are likely multiple forms of alcoholism and multiple pathways to develop alcoholism. Jellinek (3) was perhaps the first to set forth ideas about subtypes of alcoholism based on his observations of patients over many years. More recently, a variety of subtypes have been proposed, including Type I versus Type II, as described by Cloninger (91), Type A versus Type B (92), and Lesch's subtyping concepts (93). Type I/II subtypes were derived from behavioral genetic studies using adoptees and clinical populations (91). Type A/B subtypes were derived from cluster analyses applied to a battery of clinical and historical variables gathered on clinical populations (92). Lesch's typology was proposed based on longitudinal observations of alcoholic patients followed over years (93). Although 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 (94) have recommended that subtyping of alcoholic people 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 seem 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.

9.1. Biological Influences

9.1.1. Genetics

Alcoholism runs in families. This observation was noted thousands of years ago by Plutarch "One drunkard begets another" (95). Approximately four times as many children of alcoholic people become alcoholic as do children of nonalcoholic people. For years, it was unclear whether this increased rate was a familial effect or represented true genetic risk. During 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 (96), Sweden (97), and the United States (98). 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 alcoholic people may vary in the extent of genetic risk. Thus, the Type II alcoholic person (more severe form of illness) was found to have a robust genetic influence independent of environmental influence; whereas the Type I alcoholic person showed evidence for a gene–environment interaction (99).

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 versus DZ twins using various definitions of alcoholism have revealed strong evidence for a genetic component. This has been demonstrated in both male (100) and female (101) 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 to 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 seems 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.

9.1.1.1. Search for the Genes Underlying Alcoholism

Major efforts have been undertaken during 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 (102, 103). 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 heart beat, 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 (104). 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, the cholinergic muscarinic 2 receptor (105), and variants of the dopamine 2 receptor (106). 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 (105). 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 versus nonanxious, disinhibited versus inhibited, to draw a more complete picture of the alcoholisms with greater relevance to clinicians and implications for treatment.

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) (107) and 2) neurophysiological disinhibition (108). LR takes the form of reduced motor impairment and less subjective sense of intoxication after 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 (107). 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 (109).

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 (110). Since then, a broader theory of cognitive and behavioral disinhibition as a risk phenotype has emerged (108) and genetic associations to this phenotype have been reported as well (111). One intriguing observation is that this phenotype seems to be associated with conduct disorder and sociopathy, which, as noted above (see Sect. 9), are found in Type II/Type B alcoholic people.

Other phenotypes associated with risk for alcoholism have been reported, e.g., trait anxiety and 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.

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 (112). 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 (112). 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) (22, 113). 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.

9.2. Psychological Factors

An addictive personality was part of clinical parlance 30 to 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, although their effects may be mediated through psychiatric illnesses (114).

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 (section 8), 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 posttraumatic stress disorder, increase risk for alcohol use disorders, as do attention deficit disorder and depression. Unipolar depression only slightly increases risk.

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 during the past 20 years after a variety of public policy steps, including increased public awareness and stricter legal sanctions (115).

10. Treatment

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 (116). Symptoms of alcohol withdrawal usually begin in the first 12 to 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, although 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 to 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 to 96 hours after drinking has stopped. Probably less than 5% of alcoholic people experience serious withdrawal on 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, whereas 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 DTs or a seizure. Factors that increase risk include comorbid medical illness, such as acute infections, fractures, or burns, history of DTs or a seizure, longer time before treatment starts, increased severity of typical alcohol withdrawal symptoms, including systolic blood pressure greater than 145 mmHg or heart rate greater than 120 (117–121). 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) (122) has emerged as the most common assessment instrument to monitor the severity of alcohol withdrawal. The most widely used version consists of 10 questions assessing nausea, headache, tremor, sweating, anxiety, agitation, auditory disturbances, tactile disturbances, visual disturbances, and orientation. CIWA-Ar scores greater than 10 or so in the first 24 hours after cessation of alcohol indicate that medication treatment could be helpful; scores greater than 15 (119) indicate an increased risk for serious withdrawal problems (please see the CIWA addendum).

Treatment of withdrawal is generally highly effective—the mortality rate from alcohol withdrawal has been greatly reduced during the past 60 years, but not to zero. The benzodiazepines are considered the drugs of choice for withdrawal (123, 124), 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, and 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 with 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, although they have clear risks as well (124).

Administration of thiamine and other B vitamins is obligatory in the treatment of alcohol withdrawal. Thiamine deficiency is known to contribute to Wernicke–Korsakoff syndrome and its administration can prevent the irreversible memory deficits seen in Korsakoff's syndrome. Thiamine is poorly absorbed from the gastrointestinal tract in alcoholism, therefore IM or IV doses of adequate amount, e.g., 100–200 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, alcoholic people usually are not dehydrated; actually, they may be overhydrated from consumption of large volumes of fluid (125).

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 exclude 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.

10.2. Postdetoxification 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, although the key goal is to help the alcoholic person maintain sobriety and reduce the impact of relapses. O'Brien and McLellan (126) 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 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, although this has been used with some success, particularly in patients with less severe dependence (127).

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 (128), 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 or abuse and in their readiness to change. Prochaska and DiClemente (129) 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.

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 (130). 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 used 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, although 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. (128), in a randomized, controlled study, found that two brief interventions of 10 to 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, 4-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 emergency department visits, and an overall savings of $43,000 in health care costs for every $10,000 invested in the intervention (131). 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.

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 (132). This randomized trial gathered a wide range of assessments, e.g., drinking patterns, psychiatric symptoms, on 1,726 alcoholic subjects who entered the study after residential treatment (aftercare) or as outpatients. Subjects were randomly assigned to one of three treatments provided during 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 3 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 (133). 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.

10.2.2. Alcoholics Anonymous and Other Self-Help Groups

Alcoholics Anonymous (AA) has been widely viewed as providing more help for alcoholic people than any other approach. AA was started in the 1930s by two alcoholic people, 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 alcoholic people 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 approximately 1.1 million AA members in the United States in approximately 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, thus, 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 (132). However, probably no more than 5% of alcoholic individuals are active in AA.

There is no question that AA provides help for many alcoholic people that they cannot obtain elsewhere. No doubt it has saved many lives. Most clinicians who treat alcoholic people 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. Almost everyone agrees that AA should be given a fair opportunity.

Clinicians should also consider referring family members of the alcoholic person 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 person is in treatment. As family members become educated regarding alcoholism, they can feel empowered and, sometimes, help the alcoholic person 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 use techniques similar to cognitive–behavioral therapy and do not call on 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 and Women for Sobriety.

Clinicians should be aware of these alternative self-help programs and whether they are available in their area.

10.2.3. Medication Treatment

The use of medications to treat alcoholism entered a new phase in 1995, with the FDA approval of naltrexone. Before then, the only FDA-approved medication for alcoholism was disulfiram (Antabuse®).

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 heart beat, low blood pressure, nausea, and sweating. This experience can be severe and, in vulnerable individuals, several fatalities have been reported (134). 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 (135). 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 very 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 Veteran's Administration (VA) study of 605 subjects (136). In that study, 250 mg of disulfiram was blindly compared with 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 (137), such as by a spouse or treatment center. Overall, the evidence suggests that disulfiram has value in the treatment of alcoholism (138). Clearly, patients must be motivated to take disulfiram, preferably under some form of supervised use. Patients need to be warned regarding 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.

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 (139, 140) revealed that 50 mg naltrexone reduced the risk of relapse to heavy drinking compared with placebo by about half (Fig. 14.2). Effects on abstinence were not as robust. Since these initial reports, naltrexone has been studied in approximately 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 (five or more drinks on one occasion for a man and four or more drinks for a woman), with marginal effects on abstinence (141–143). Reductions in drinking frequency and drinks per drinking days have also been reported. A number of studies have shown that naltrexone reduces the "high" experienced from alcohol if a lapse occurs (144), and this author has seen this happen on numerous occasions. Other reports have noted a reduction in

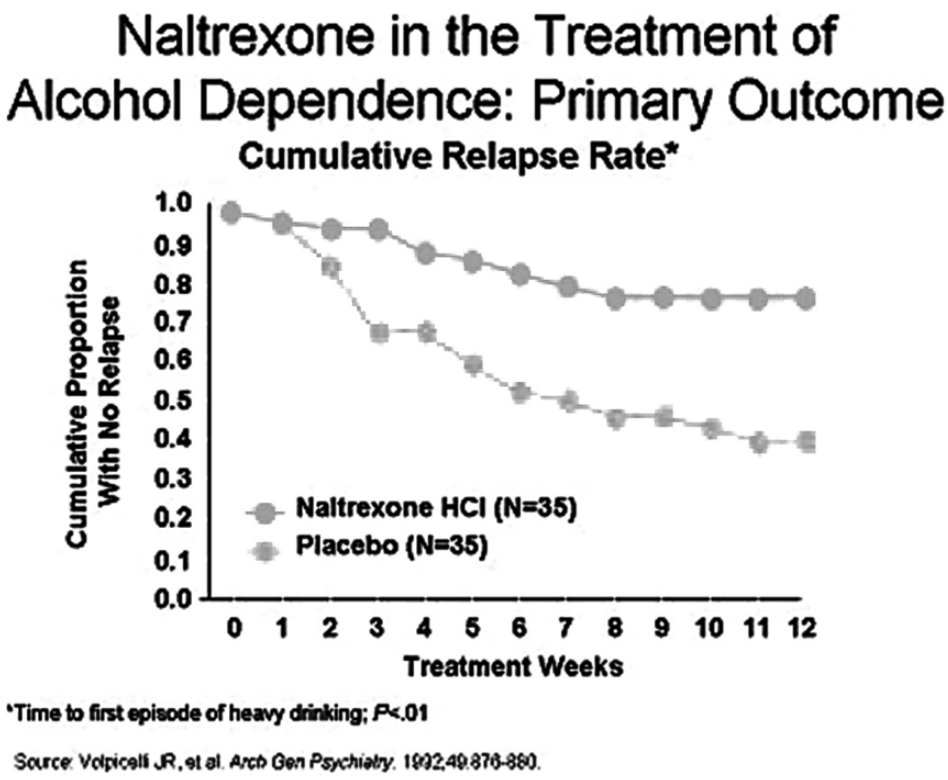

FIGURE 14.2. Naltrexone was more effective at preventing relapse than placebo. During the 12-week treatment, 23% of the naltrexone-treated patients and 54% of placebo-treated patients met the criteria for relapse defined as the clinically significant resumption of drinking. Naltrexone significantly reduced the time to relapse at the end of the 12-week treatment ($P < 0.01$) and was not associated with any psychiatric symptoms or mood changes. A small percentage of patients experienced nausea, and one naltrexone-treated patient reported increased pain from arthritis. The results from this study suggest that naltrexone may be a safe and effective adjunct to treatment in alcohol-dependent subjects, especially in the prevention of relapse (reprinted from reference (140). Copyright © 1992, American Medical Association. All rights reserved).

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 to 12 months and very possibly longer, depending on response and risk for relapse.

10.2.3.3. Acamprosate

Acamprosate is structurally related to GABA, but its mechanism of action has been proposed to be a reduction in alcohol-induced glutamatergic hyperactivity—a factor possibly contributing to protracted withdrawal (145). Clinical trials with acamprosate in more than 4,000 subjects have generally been very consistent and reveal that acamprosate increases the likelihood of complete abstinence approximately two fold (Fig. 14.3). In patients who do not maintain complete abstinence, acamprosate increases the number of abstinent days (141). The majority of acamprosate trials have been completed outside the United States in settings in which patients have established abstinence. The two clinical trials completed in the United States recruited many nontreatment-seeking patients who had shorter periods of abstinence and both of these trials were negative (146, 147). Mason et al. (146) 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 approximately 1 year to allow the patient to solidify behavioral changes.

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

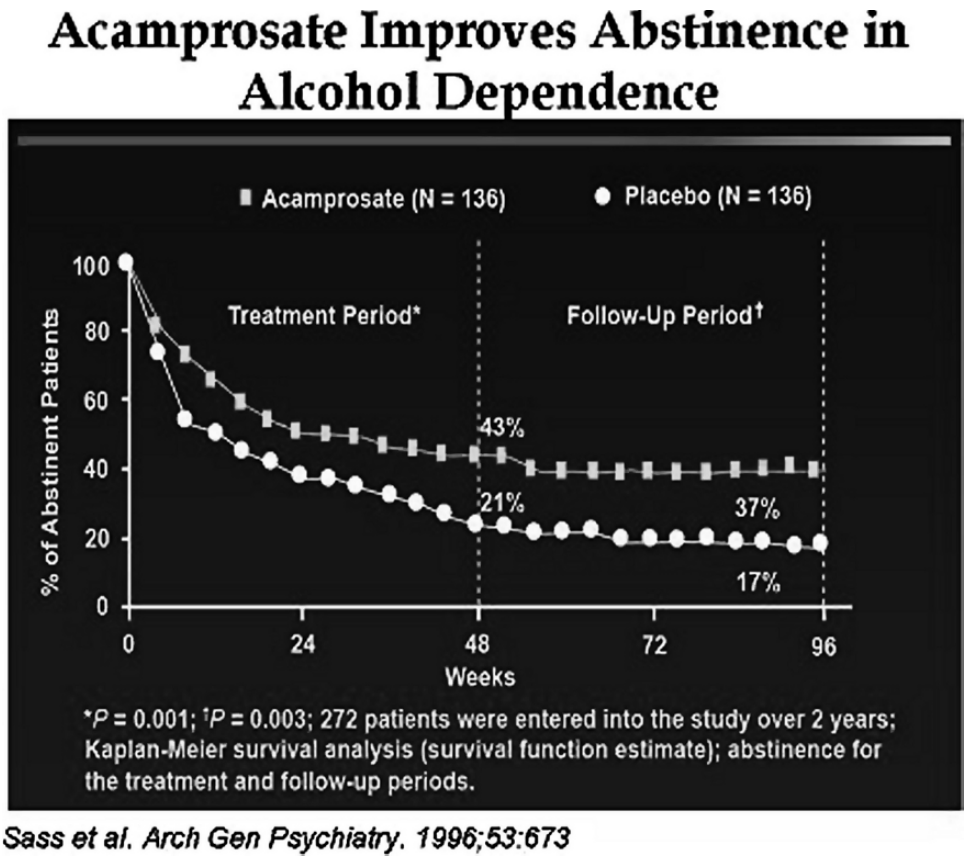

FIGURE 14.3. Acamprosate improves abstinence in alcohol dependence. Two hundred seventy-two patients were entered into the study during 2 years; Kaplan–Meier survival analysis (survival function estimate). Continuous abstinence for the treatment and follow-up period. *$P = 0.001$; †$P = 0.003$ (reprinted from reference (155). Copyright © 1996, American Medical Association. All rights reserved).

addiction. A long-acting formulation has the advantage of ensuring a steady delivery of medication even in a patient who is ambivalent regarding 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 (148, 149). Both of these studies used formulations that were administered intramuscularly at monthly intervals. The Garbutt et al. (148) study used a dose of 380 mg/month and found a main effect for LA-NTX in reducing heavy drinking by approximately 50% during a 6-month trial. Subjects who were abstinent before injection demonstrated the greatest responses and, in these subjects, LA-NTX significantly increased the likelihood of complete abstinence. Kranzler et al. (149), 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 non-heavy drinking days, although 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.

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 plus naltrexone compared with each monotherapy and with placebo. The evidence is mixed. One German study (150) found evidence for superiority of the combination compared with acamprosate or placebo but not to naltrexone. Acamprosate and naltrexone monotherapy were each superior to placebo. A trial in the United States (147) 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

Clinical Institute Withdrawal Assessment of Alcohol Scale, Revised (CIWA-Ar)

Patient: _____ **Date:** _____ **Time:** _____ (24 hour clock, midnight = 00:00)

Pulse or heart rate, taken for one minute: _____ **Blood pressure:** _____

NAUSEA AND VOMITING – Ask "Do you feel sick to your stomach? Have you vomited?" Observation.

0 no nausea and no vomiting
1 mild nausea with no vomiting
2
3
4 intermittent nausea with dry heaves
5
6
7 constant nausea, frequent dry heaves and vomiting

TACTILE DISTURBANCES – Ask "Have you any itching, pins and needles sensations, any burning, and numbness, or do you feel bugs crawling on or under your skin?" Observation.

0 none
1 very mild itching, pins and needles, burning or numbness
2 mild itching, pins and needles, burning or numbness
3 moderate itching, pins and needles, burning or numbness
4 moderately severe hallucinations
5 severe hallucinations
6 extermelly severe hallucinations
7 continuous hallucinations

TREMOR – Arms extended and fingers spread apart. Observation.

0 no tremor
1 not visible, but can be felt fingertip to fingertip
2
3
4 moderate, with patient's arms extended
5
6
7 severe, even with arms not extended

AUDITORY DISTURBANCES – Ask "Are you more aware of sounds around you? Are they harsh? Do they frighten you? Are you hearing anything that is disturbing to you? Are you hearing things you know are not there?" Observation.

0 not present
1 very mild harshness or ability to frighten
2 mild harshness or ability to frighten
3 moderate harshness or ability to frighten
4 moderately severe hallucinations
5 severe hallucinations
6 extremely severe hallucinations
7 continuous hallucinations

PAROXYSMAL SWEATS – Observation.

0 no sweat visible
1 barely perceptible sweating, plams moist
2
3
4 beads of sweat obvious on forehead
5
6
7 drenching sweats

VISUAL DISTURBANCES – Ask "Does the light appear to be too bright? Is its color different? Does it hurt your eyes? Are you seeing anything that is disturbing to you? Are you seeing things you know are not there?" Observation.

0 not present
1 very mild sensitivity
2 mild sensitivity
3 moderate sensitivity
4 moderately severe hallucinations
5 severe hallucinations
6 extremely severe hallucinations
7 continuous hallucinations

ANXIETY – Ask "Do you feel nervous?" Observation.

0 no anxiety, at ease
1 mild anxious
2
3
4 moderately anxious, or guarded, so anxiety is inferred
5
6
7 equivalent to acute panic states as seen in severe delirium or acute schizophrenic reactions

HEADACHE, FULLNESS IN HEAD – Ask "Does your head feel different? Does it feel like there is a band around your head?" Do not rate for dizziness or lightheadedness. Otherwise, rate severity.

0 not present
1 very mild
2 mild
3 moderate
4 moderately severe
5 severe
6 very severe
7 extremely severe

AGITATION – Observation.

0 normal activity
1 somewhat more than normal activity
2
3
4 moderately fidgety and restless
5
6
7 paces back and forth during most of the interview, or constantly thrashes about

ORIENTATION AND CLOUDING OF SENSORIUM – Ask "What day is this? Where are you? Who am I?"

0 oriented and can do serial additions
1 cannot do serial additions or is uncertain about date
2 disoriented for date by no more than 2 calendar days
3 disoriented for date by more than 2 calendar days
4 disoriented for place/or person

Total **CIWA-Ar** Score _____
Rater's Initials _____
Maximum Possible Score 67

 This assessement for monitoring withdrawal symptoms requires approximately 5 minutes to administer. The maximum score is 67 (see instrument). Patients scoring less than 10 do not usually need additional medication for withdrawal.

Sullivan, J.T.; Sykora, K.; Schneiderman, J.; Naranjo, C.A.; and Sellers, E.M. Assessment of alcohol withdrawal: The revised Clinical Institute Withdrawal Assessment for Alcohol scale (**CIWA-Ar**). *British Journal of Addiction* 84: 1353–1357, 1989.

the combinations seem tolerable although 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 in which outcomes are less than satisfactory, consideration should be given to combining acamprosate and naltrexone/LA-NTX.

10.2.3.6. 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, to date, no findings have emerged that can be readily translated to the clinic. In a preliminary study, Oslin et al. (151) 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.

10.3. Overall Effectiveness of Treatment for Alcoholism

O'Brien and McLellan (126) noted that one of the myths regarding 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 person. 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 (126) argue that 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 (152).

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. (153) examined seven large multisite studies that systematically tracked outcomes. One year after treatment, approximately 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. (152) and by O'Brien and McLellan (126) is that treatment is effective for many patients and far too many patients never receive treatment.

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 over time, 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 (154). 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" (1; p.11).

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15
Drug Addiction

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Abstract Drug addiction 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 of drug addiction. Pathologic consequences from drugs of abuse (e.g., opioids, sedatives, amphetamines, cocaine, cannabis, nicotine, phencyclidine [PCP], hallucinogens) are explained as well. The understanding of drug addiction has improved with 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 · Behaviors · Course · Drugs of abuse · Treatment

1. Definition

Drug addiction is a serious public 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). Repeated drug use causes plasticity in the brain in patients with drug addiction who tend to relapse easily in the context of environmental cues, cravings, or stress. Despite significant negative consequences, drug-dependent patients are unable to control their drug use.

Drug addiction is described as "substance dependence" in the fourth edition of *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV) (see Table 15.1) (3). Both Substance Dependence and Substance Abuse involve a maladaptive pattern of substance use with consequences occurring within a 12-month period. Substance Dependence may occur with physiological dependence, as manifested either 1) by markedly increased tolerance and/or diminished effect from the customary dosage, or 2) by withdrawal syndrome and/or use of a related substance to relieve withdrawal. Substance Dependence may also occur without physiological dependence, in which case the individual manifests three or more of the following:

- Compulsive use characterized by taking a larger amount or for a longer time than intended
- Persistent craving or inability to cut down or control use
- Spending a great deal of time obtaining and/or using the substance
- Giving up important social–occupational–recreational activities in favor of using
- Continued use despite knowledge of having a physical or psychological problem caused or exacerbated by use

Substance Abuse involves continued or recurrent substance use associated with one or more of the following:

- Failure to fulfill major role obligations at work, school, or home
- Use in situations that are physically hazardous (such as driving)
- Legal problems (such as arrest)
- Social or interpersonal problems caused or exacerbated by use (e.g., arguments, fights)

Pharmacologic considerations must be included in the diagnosis, but clinical judgment still must be applied regardless of drug dosage. For example, mixed drug abuse, mental retardation, dementia, other psychiatric conditions, and extreme youth or older age may lead to drug-related problems at doses lower than usual. Even relatively mild psychoactive compounds, such as caffeine or nicotine, 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. Substance dependence usually involves the presence of tolerance to the drug

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TABLE 15.1. Diagnostic criteria for substance dependence and substance abuse according to the DSM-IV.

	Criteria
Substance dependence or abuse	A maladaptive pattern of substance use, leading to clinically significant impairment or distress, occurring within a 12-month period
Substance dependence	Three (or more) of the following must be present: 1. Tolerance: (a) need for markedly increased amounts of the substance to achieve intoxication or desired effect; (b) markedly diminished effect with continued use of the same amount of the substance 2. Withdrawal: (a) withdrawal symptoms; (b) substance use to relieve or avoid withdrawal symptoms 3. Substance use in larger amounts or over a longer period 4. Unsuccessful efforts to cut down or control substance use 5. A great deal of time is spent to obtain the substance or recover from its effects 6. Important social, occupational, or recreational activities are given up or reduced because of substance use 7. Continued substance use despite physical or psychological problem caused by the substance
Substance abuse	One (or more) of the following must be present: 1. Recurrent use resulting in a failure to fulfill major role obligations at work, school, or home 2. Recurrent substance use in physically hazardous situations 3. Recurrent substance-related legal problems 4. Persistent/recurrent social or interpersonal problems

or withdrawal on 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, and insomnia

Sedatives: Nausea, vomiting, malaise, weakness, tachycardia, sweating, hypertension, anxiety, depressed mood or irritability, orthostatic hypotension, coarse tremor and possible disorientation, hallucinations, and convulsions in severe cases

Stimulants: Fatigue, disturbed sleep, unpleasant dreaming, increased appetite

Nicotine: Craving, irritability, anxiety, depression, difficulty concentrating

Onset of abstinence symptoms after the last dose varies with the drug's duration of action. Withdrawal can begin in 4 to 6 hours with short-acting drugs (e.g., lorazepam, heroin, morphine), in 8 to 16 hours with intermediate-acting drugs (e.g., opium, methadone, phenobarbital), or in several days with long-acting drugs (e.g., ethchlorvynol, diazepam). Cannabis does not have a distinct withdrawal syndrome. However, chronic heavy users do 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 caused by storage of active cannabis fractions (e.g., tetrahydrocannabinol) in body fat stores, with gradual excretion over days or weeks.

DSM-IV includes the diagnosis of nicotine dependence, but not nicotine abuse. Nicotine dependence includes the nicotine withdrawal syndrome, unsuccessful attempts to stop or reduce its use, or continued use despite a serious nicotine-related physical disorder (e.g., emphysema, coronary artery disease, Berger's arterial disease).

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 caused by a medical condition or substance may accompany drug use. Depending on duration and pattern of drug use, these diagnoses may or may not be accompanied by drug addiction.

2. Etiology and Pathogenesis

Other than excessive or problematic drug use as a final common pathway, there is no one cause of drug abuse. Rather, drug abuse is multifactorial in its etiology. The public health model of agent (drug), host (drug-using individual), and environment (society) has proven useful in conceptualizing the complex causes of drug abuse.

2.1. Host Factors

2.1.1. Family–Genetic Influences

Similar to many other psychiatric disorders, drug abuse tends to occur within the same family. This suggests that genetic factors may play a role in drug addiction. One family study reported an eightfold increased risk of substance disorders in relatives of probands with substance disorders (4). Twin and adoption studies have also demonstrated that substance disorders are correlated with genetic and environmental factors (5–7). Genetic factors have been seen as accounting for 30 to 70% of the variance in the clinical features of drug addiction. Offspring of heavy tobacco smokers are considerably more apt to become nicotine 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 (9). Similarly, drug-dependent persons in the United States often have alcoholic relatives, as well as depressed or manic relatives.

Several genes contribute to the vulnerability to addictions. The genetic variants of the following genes have been reported to induce addiction vulnerability: the genes encoding the μ-opioid receptor (OPRM-1), in alcoholism and heroin addiction (10, 11); catechol-O-methyltransferase (COMT), in heroin, stimulant, nicotine, and alcohol dependence (12); dopamine D4 receptor (DRD4), in alcohol, heroin, and stimulant addiction (13); and serotonin transporter (SERT), in alcohol, nicotine, and heroin addiction (14).

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 (15). 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—pleasure molecule—in the reward circuit. 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 in the reward circuit (16). Other areas involved in drug addictions are the prefrontal cortex (e.g., orbitofrontal cortex, anterior cingulate), lateral basal amygdala, and extended amygdala (e.g., bed nucleus of stria terminalis, central medial amygdala) (17). 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 because of negative reinforcement (increasing addictive behaviors to remove the aversive states) in the later stage of addiction (18).

2.1.3. Psychological Variables

Psychological and personality traits usually accompany drug abuse, 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 (19). No one personality type predates drug abuse, although those with chronic pain, anxiety, depression, mania, psychosis, inattention, hyperactivity, impulsiveness, and/or antisocial attitudes seem to be at greater risk. Personality characteristics of drug abusers, perhaps as much acquired as primary, typically include hostile dependence, low frustration tolerance, limited flexibility and adaptiveness, low self-esteem, risk taking, and novelty seeking (20).

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 (21). 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 (22). 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 (23).

2.2. Agent Factors

2.2.1. Pharmacology of Drugs of Abuse

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 may aid in blocking out distressing thoughts or feelings. Symptoms relieved by drugs of abuse include pain, 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 drugs (e.g., methadone, clonazepam). Modes of administration with liability for drug abuse include intravenous injecting, smoking, and snuffing, which produce quicker drug effect than subcutaneous injection or ingestion.

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 nicotine. Cessation of drug use in the tolerant individual precipitates withdrawal, a morbid state that persists hours, days, or 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, 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 drug dependence, drug usage may continue more to avoid withdrawal than to achieve intoxication.

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 seek relief 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 (24). 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 caused largely by 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.

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 can afford them.

2.3. Environmental or Social Factors

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 Moslem nations that forbid alcoholic beverages 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 opiate dependence.

Patterns of use for a particular drug determine the likelihood that the drug will be associated with abuse. Nonritual use away from family, in a surreptitious fashion, with intoxication as a goal may be pathogenic. Safe use is more apt to occur 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 is an example (25).

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., nicotine, 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).

2.3.2. Drug Laws

Antidrug laws began to appear several hundred years ago. Before 1500 AD, the Aztecs strictly controlled alcohol use by dose, frequency, and social status. Asian and European kingdoms enacted laws regarding nicotine and opium. Antidrug legislation accelerated in the 18th to 20th centuries. We are still in the era of drug diffusion, because modified drugs (e.g., cocaine from coca, heroin from opium) and new manufactured drugs (e.g., synthetic opioids, sedatives, hallucinogens) 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, commercial, religious, and ethnic sectors, can exacerbate drug problems by driving drug production, distribution, and use into a criminal subculture.

3. Epidemiology

3.1. Methods of Study

Epidemiologic assessment is key in measuring the extent of drug abuse, 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 10 arrested addicts is known to have previously received care at the treatment facility and 100 addicts are arrested, then the capture–recapture method would suggest that 1000 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.

3.2. Rates of Drug Abuse

Rates of drug abuse often fluctuate widely over time and from place to place. An epidemiologic study in the early 1980s indicated that 5 to 6% of adults had drug dependence at some point in their lives (26, 27). Several opioid and amphetamine "epidemics" have occurred during the last half-century. Nicotine dependence increased progressively during the last century among men and, more recently, among women, although rates among men have been declining. Cannabis abuse increased markedly during the late 1960s but has declined somewhat since then, while still being widely used. Cocaine abuse and dependence have 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.

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 has occurred predominantly among women. In recent years, the rates of nicotine and alcohol 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 (28).

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, even students have been able to afford cannabis and other drugs.

Medical workers are especially liable to abuse of 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.

4. Pathology

Pathologic consequences from drug abuse vary widely with the drug, dosage, duration of use, and route of administration.

4.1. Opioids

Although opioid drugs differ considerably in dosage (Table 15.2) and duration of action, the maximal potencies of the stronger opioid drugs (e.g., morphine, heroin, fentanyl, methadone) are very similar. Weaker opioids (e.g., codeine, propoxyphene) cannot equal them, even in large doses. Some opioids, such as pentazocine, have mixed agonist–antagonist effects, so that increasing the dose can precipitate withdrawal symptoms. Combined buprenorphine–naloxone discourages parenteral use, which would precipitate withdrawal in an opioid dependent person.

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. Although 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, hypotension, and lethargy. Coma and possibly death by respiratory depression can result from overdose. The withdrawal syndrome, beginning 4 to 12 hours after the last dose (depending on the drug and dose), consists of agitation, piloerection, dilated pupils, muscle aches, and abdominal cramps. 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 (29).

4.2. Sedatives

These drugs include the benzodiazepines, barbiturates, glutethimide, methaqualone, chloral hydrate, paraldehyde, and ethchlorvynol. Although showing cross-tolerance with

TABLE 15.2. Dose equivalents of opioid drugs.

Drug	Dose equivalent (mg)		Dosing interval (h)
	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	20	10	6–8
Oxycodone	20	15[b]	3–4

[a]NA, not available (50 μg/h patch).
[b]Dose change made by the editor.

TABLE 15.3. Dose equivalents of benzodiazepines.

Drug		Dose equivalent (mg)	Half-life (h)
Generic	Trade		
Alprazolam	Xanax	0.25[a]	12
Chlordiazepoxide	Librium	10[a]	100
Clonazepam	Klonopin	0.5[a]	34
Diazepam	Valium	5	100
Lorazepam	Ativan	1	16
Midazolam	Versed	1.5	3
Oxazepam	Serax	15	8
Temazepam	Restoril	5[a]	11
Triazolam	Halcion	0.1[a]	2

[a]Dose change made by editor.

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.

Benzodiazepines and barbiturates act on the ionotropic γ-aminobutyric acid (GABA) type A receptor. When substances are attached to the GABA receptor, GABA opens the chloride channel, making 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. Similar to 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. 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 with the long-acting sedatives (30).

4.3. Amphetamines and Similar Drugs

These drugs (including methylphenidate) are often abused by night workers, those doing prolonged repetitive work (e.g., truck driving), or chronically dysthymic individuals. Amphetamines facilitate the release of 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, 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 after withdrawal, may be a withdrawal effect, a sign of an emerging primary depression, or some combination of both (31).

4.4. Cocaine

Similar to amphetamines, cocaine abuse is apt to ensue in the user who is bored, fatigued, or depressed. Because 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 obtain the drug effect. Under such circumstances, the cost of a cocaine habit mounts 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 (32). Despite cocaine's brief duration of action, its metabolite, benzoylecgonine, remains detectible in urine for a few days after 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 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 for minutes rather than hours. Certain complications resemble those of amphetamine use, such as paranoia, hallucinations, or hypertension.

4.5. Cannabis

Although numerous psychoactive compounds exist in cannabis, most of its effect appears to be caused by delta-9-tetrahydrocannabinol. Cannabinoids bind to the cannabinoid receptors (33). Potency of cannabis preparation varies with proximity 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. These include dry mouth, increased appetite, tachycardia, injected conjunctivae, and relaxation. Coordination for simple

tasks is not impaired at lower doses, although balance 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. Short-term memory loss leads to disjointed thinking, with consequent silliness, social withdrawal, or panic.

Some tolerance occurs with chronic use, but a distinct withdrawal syndrome has not been described. Because tetrahydrocannabinol is stored in fat, chronic users may excrete the drug for days or even weeks after the last use.

4.6. Nicotine

Whether consumed by smoking, snuffing, or chewing, tobacco's psychoactive effect is largely caused by nicotine. Similar to 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 approximately 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, for 20 years). Although nicotine dependence is notoriously difficult to reverse permanently, physician recommendations to cease nicotine use are effective. During nicotine cessation, obesity is a frequent complication (34).

4.7. Caffeine

In lower doses of 50 to 150 mg, caffeine reduces fatigue and enhances mental activity while causing some tachycardia, vasodilation, and diuresis. It produces these effects by stimulating catecholamine release. Higher doses (i.e., more than 600 mg/d) may produce excitement, agitation, headache, irritability, and insomnia. Withdrawal symptoms in high-dose users (i.e., more than 1000–1200 mg/d) can include fatigue and somnolence (35).

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 is also present in many over-the-counter and prescription drugs taken for pain, appetite suppression, and the common cold. Excessive caffeine use can cause similar features of caffeine dependence, such as withdrawal or tolerance (36).

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, because 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 (37). 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 (38). Endemic and epidemic use has prevailed among children during the last three decades. Originally reported in American Indian and Hispanic communities (39), it has spread to other ethnic communities.

4.9. Phencyclidine

Phencyclidine (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 because of enterohepatic recirculation. Acute and chronic users may present to emergency rooms with various psychiatric syndromes from panic attack, to mania, schizophreniform psychosis, and delirium (40).

4.10. Hallucinogens

These include natural substances (e.g., peyote, morning glory seeds) and synthetic compounds (e.g., n-lysergic acid [LSD]). LSD functions as a partial agonist at the serotonin type 2 (5-HT2) receptor. Altered perceptual states are produced, and

panic, hallucinations, and delusions may occur. Although the half-lives of these drugs are only a few hours, psychic effects may persist for 6 to 12 hours. Hallucinosis can continue for a few to several days in unusual cases. Vulnerable individuals can experience first episodes or recurrences of mania, schizophreniform psychosis, delusional disorder, or schizophrenia. Physical manifestations are few, except for possible anticholinergic toxicity (40).

5. Clinical Picture

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 the 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 very early in their course or in severely advanced stages. The problem may be acute or chronic, life threatening or minor, and readily discerned or vague and difficult to define.

5.2. Data Collection

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 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.

Because drug abuse may present with various surgical, medical, or psychiatric problems, the clinician will want to inquire routinely regarding each patient's use of drugs. To rule drug abuse in or out, the physician must know each patient's drug use type (if present), dose, duration, and pattern of use and route of administration.

Drug-abusing patients typically do not volunteer symptoms indicative of depression, anxiety, panic, or psychosis. Specific inquiry is necessary.

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.

5.2.1. Case Report

A 14-year-old girl had been sniffing gasoline for approximately 2 hours per day, two to four times per week, during the previous 3 years. She had observed groups of other children in the neighborhood engaging in this practice, although she practiced it alone. Around the time that she began using, her alcoholic father had abandoned the family, and her mother was largely absent, working two jobs. Recently, her mother had begun to drink excessively at home. She presented after having written a suicide note. Formerly an A/B student, her current school grades were Ds and Fs. Mental status examination revealed impaired orientation, memory impairment, concrete thinking, and extreme irritability. After detoxification and a period of observation, psychological testing indicated borderline intelligence and signs of organic impairment.

This case exemplified an early onset case in a context of family upheaval and familial alcoholism. Early on, her use of inhalants helped her to cope with emotional distress while functioning as a student and eldest daughter of three children. With time, the abuse led to cognitive changes and loss of academic achievement, which had earlier sustained her flagging self-esteem. Subsequent testing suggested permanent loss of her former intellectual capacity.

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. The initial problems associated with chronic use tend to be caused by psychosocial and neuropsychiatric complications. Socioeconomic deterioration, increasing family alienation and social withdrawal, progressive (rather than static) sociopathy, and legal problems should raise the index of suspicion for drug abuse.

Special clinical presentations depend on the patient's age, drug, and the setting. Apathy, anergy, and decline in grades predominate among adolescents and young adults. Their

families report anger, oppositional behavior, and personality change. Later in adulthood, Monday morning absenteeism, reduced productivity, and injuries occur in the workplace. Their family members and friends may observe social withdrawal or secretive behavior. In clinical settings, nurses or physicians may note drug-seeking behaviors, with symptomatic complaints out of proportion to physical or laboratory findings.

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, and 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). Drugs that are more potent (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., nicotine) or neuropsychiatric complications (e.g., phencyclidine) as their first manifestation, whereas others are more apt initially to produce psychosocial consequences (e.g., sedatives, opioids). Drugs with potent effects, rapid onsets, and shorter half-lives (e.g., cocaine, heroin) lead to treatment within approximately 3 years of initiating their drug abuse; whereas drugs with less potent effects, slower onsets, or longer half-lives (e.g., diazepam, opium) may continue to be abused for 10 years or longer before treatment results.

Age at onset influences the course, therefore opioid dependence beginning at age 15 years affects the patient's life course differently from opioid dependence beginning at age 25 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 coming to treatment usually have more biomedical problems and social isolation; younger drug abusers experience more legal, occupational, and family problems.

Tables 15.4 to 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 usually, but not always, alters the natural course of drug abuse. 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.

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 restabilization (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

TABLE 15.4. Phases of chemical dependency: psychologic factors.

Characteristic	Early phase: problematic usage	Middle phase: chronic dependence, addiction	Late phase: deterioration
Motivation	Uses to enjoy, build up confidence, relieve insomnia, 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, remorseful	Personality change, increasing emotional lability; ambivalent about usage; feels guilty, resentful, inadequate, inferior	Erratic, suspicious, 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 chemical dependency: behavioral factors.

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, 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, disheveled dress; lack of interest in appearance; unconcern with opinions of others

TABLE 15.6. Phases of chemical dependency: social factors.

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, taking advantage; breaks promises, 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, 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, manslaughter
Finances	Spends family funds on drug or alcohol; may take extra job to support habit; may become extravagant	Spends 1/4 to 1/2 of annual income on drugs or alcohol; heavily in debt, 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 of school age.

stability in the final phase of recovery may require a few to 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 nicotine (in the absence of ongoing outpatient treatment) are remarkably similar, as shown in Fig. 15.1. Modern treatment methods have not changed the shape of this curve appreciably, although the 1-year recovery rate tends to be higher than the 20 to 35% depicted in Fig. 15.1.

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

TABLE 15.7. Phases of chemical dependency: biomedical factors.

Characteristic	Early phase: problematic usage	Middle phase: chronic dependence, addiction	Late phase: deterioration
Pharmacology	Tolerance increases; larger doses used to relax, 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, burns	Infections: respiratory, urogenital, skin; injuries; accidental overdosage; suicide attempts	Septicemia, pulmonary edema, endocarditis; alcohol users: 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, 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

TABLE 15.8. Phases of chemical dependency: treatment approaches.

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	Self-help groups; marital, family therapy; selective use of pharmacotherapy for 1–2 years (e.g., antidepressants, Antabuse); partial hospitalization (e.g., day only, evening only, weekend only)	Initial residential treatment: hospital unit, therapeutic community, halfway house, followed by some outpatient treatment methods as in "early phase"	Long-term residential treatment: special long-term units, nursing home, quarterway house, followed by "middle" and "early" treatment methods in selected cases
Prognosis with treatment	Optimal: 60–80% "significantly improved" at 1 year posttreatment	Fairly good: 40–60% "significantly improved" at 1 year posttreatment	Poor: 10–20% 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, follow treatment recommendations	Does not enter treatment unless pressured by family, employer, court, friends, physician	Will not undertake abstinence voluntarily; must be coerced by society (e.g., incarceration, legal commitment into treatment

assess the extent of impairment produced by drugs, such as hypovitaminosis or secondary infections from parenteral drug administration. 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 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 to 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 (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

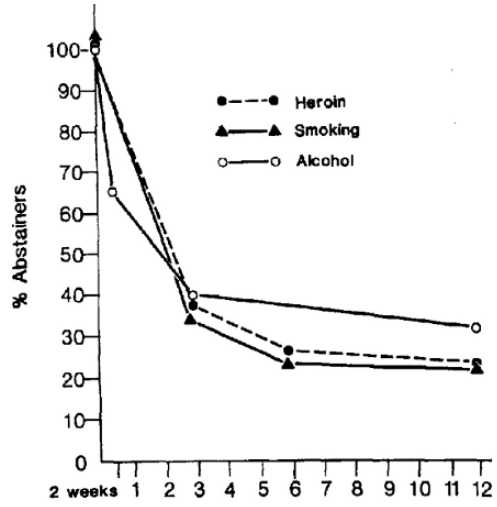

FIGURE 15.1. Relapse rate over time for heroin, smoking, and alcohol (from reference 41).

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 test results, electrolyte disturbances, hyperglycemia or hypoglycemia, and/or an abnormal dexamethasone suppression test result. 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.

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 results have been abnormal previously.

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 approximately 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). Alternatively, 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 similar to 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 schizophreniform psychosis, manic psychosis, or delirium caused by a medical condition.

Drugs also may precipitate psychiatric syndromes, which persist well beyond the drug effect in the body. 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:

8.1. Case Report

A 19-year-old college student became acutely and floridly psychotic after 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 electroconvulsive therapy (ECT) and subsequent antipsychotic treatment. A discharge diagnosis of schizoaffective disorder was made. During the subsequent year, her medication was reduced without incident. She later completed graduate school, worked for a few years, and married. Within weeks after the birth of her third child, at age 31 years, 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 caused by substances, with confusion and delirium. Chronic brain

syndrome caused by 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 caused by falls or fights. Caffeine and nicotine may produce chronic brain syndromes indirectly as a result of secondary medical complications (e.g., hypertension, emphysema).

9. Treatment

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 two drug types liable to abuse: opioids and anticholinergics. 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). For the treatment of benzodiazepine overdose, flumazenil can be used as the benzodiazepine antagonist. Gastric lavage and charcoal remain cornerstones for most drug overdoses. 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 regarding giving up drug dependence, to enter treatment. Opioid and sedative withdrawals are managed by using a drug that is cross-tolerant with the drug being abused. Some clinicians use tricyclic drugs for more severe cases of stimulant withdrawal, but minimal pharmacotherapy is needed in most of the stimulant withdrawals. 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, because 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. 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, 5-day withdrawal regimens are adequate for resolution of acute symptoms. Intermediate-acting drugs, such as clonazepam or opium, require 10 to 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, 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 for a 10-day withdrawal. Some mild insomnia or discomfort may still occur during withdrawal treatment. Patients should be dissuaded from seeking sedatives, analgesics, antiemetics, and other symptom-relieving drugs, because these may mask underlying medical or psychiatric disorders that should be identified and managed appropriately.

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. At 5 mg administered four times a day, the half-life resembles that of morphine (3 to 4 hours). Repeated daily doses greater than 20 mg/day gradually increase the half life to 12 hours and beyond. Nontolerant individuals may experience respiratory depression at doses in the 30 to 40 mg range. Clinicians using methadone for opioid withdrawal treatment should be experienced, because fatal iatrogenic overdoses have resulted in the hands of clinicians unfamiliar with opiate withdrawal manifestations or methadone pharmacokinetics. Alpha2-adrenergic agonists (e.g., clonidine, lofexidine) are other options to alleviate opioid withdrawal by controlling autonomic symptoms (42). 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).

Referral to special drug treatment programs may be necessary if those providing early medical care do not have resources 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.

9.2. Assessing the Phase of Recovery

The following phases of treatment entry and recovery have been described and subsequently validated (43):

- 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 move the patient from precontemplation to contemplation.

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 rock 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 years, he had recently moderated his use after the suicide death of his best friend several weeks earlier. He initially refused referral to care, because he thought his drug use was not out of control. The emergency room (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 dialog 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 caused by 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).

9.3. Treatment Modalities

Modalities for treatment of drug abuse are numerous and include the following:

Psychotherapies and sociotherapies: Individual, couples, family, and group; relapse prevention; motivational enhancement therapy, verbal aversion; contingency contracting; social skills learning; and day, evening, or weekend programs; this approach assumes 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 for relapse prevention. For the treatment of severe opioid dependence, methadone maintenance program has been most successful to decrease illicit opioid consumption as well as medical, social, and legal consequences related to opioid use. In 2002, another medication, buprenorphine, a partial μ-opioid agonist and a κ-opioid antagonist, was approved by the US Food and Drug Administration (FDA) for treating opioid dependence. Buprenorphine can be prescribed in a primary care office setting instead of highly regulated methadone programs. Buprenorphine has less abuse potential and a better safety profile than methadone. During the induction phase, buprenorphine is initiated while monitoring the patient daily for 3 to 7 days until a stable dose is reached. Typically, the induction doses are 2 to 8 mg. During the maintenance phase, most patients take between 8 and 32 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 and monitoring are required to increase compliance with naltrexone (44). Several medications have been approved by the FDA for alcohol dependence: disulfiram, naltrexone, acamprosate, and long-acting injectable naltrexone (see Chap. 14). No medication has been approved by the FDA for the treatment of cocaine dependence, but several medications have been reported to be effective in clinical trials. These agents work by increasing dopamine levels (disulfiram, amantadine, bromocriptine), enhancing the GABA system (baclofen, carbamazepine, tiagabine), or decreasing adrenergic activities (propranolol) (45,46). For nicotine dependence, several medications have been approved by the FDA and are widely used in primary settings. These interventions include nicotine replacement therapy (transdermal nicotine patch, gum, nasal spray, nicotine inhaler, lozenge) or nonnicotine oral agents (bupropion, varenicline tartarate). Nicotine (47) and cocaine vaccines (48) have also been under investigation.

Somatotherapies: electroacupuncture (49).

Residential: Special recovery-oriented residential facilities, halfway houses, and therapeutic communities; these

alternatives can be useful for the unemployed or homeless patient.

Properly speaking, self-help programs are not a form of treatment, although they may be therapeutic. They include Narcotics Anonymous (primarily for illicit drug abusers), Alcoholics Anonymous (primarily for abusers of prescribed or licit drugs, as well as alcohol), Alanon (for relatives of drug abusers), and other drug-specific, ethnic-specific, sex-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, they will probably not resolve spontaneously. Continuation of major depression, schizophreniform psychosis, mania, and other major disorders beyond 2 weeks almost always calls for specific treatment 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.

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 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 maintenance programs can help selected patients.

Treatment success is related to many factors besides treatment modalities themselves. As indicated in Table 15.8, matching the 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 the following characteristics vis-a-vis treatment:

- Occupied as employees or students
- Residence with the family or with sober persons
- Treatment-seeking earlier rather than later
- Compliance with treatment recommendations
- Involvement of the family in treatment
- Continued treatment or self-help on a regular basis during 1 or more years
- Pharmacotherapy, as warranted and appropriate to the case; pharmacological interventions improve relapse prevention 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 easily after addiction treatment. Proper evaluation and treatment of comorbid psychiatric disorders can contribute to relapse prevention

Acute detoxification and medical management alone tends 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 after discharge is low, usually approximately 0 to 15%. With continued outpatient care, plus case management in severe cases, the rate of abstinence at 1 year can range from approximately 20 to 40%, and can be even higher under optimal conditions. Because those who are abstinent and doing well at the end of 1 year have good outcomes in most cases, the first year of outpatient care is most critical (50).

Cost/benefit from treatment also must be considered. For unemployed or destitute patients, society must provide the care, and society must be assured that its funds are well spent. Most public programs have limited funds for treatment and rehabilitation, so that close coordination must transpire between professional resources and community-based, patient-centered, recovery resources.

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16
Sexual Disorders: Dysfunction, Gender Identity, and Paraphilias

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Abstract Sexual disorders in the *Diagnostic and Statistical Manual*, fourth edition, text revision (DSM-IV-TR) 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 review the diagnostic criteria, prevalence, etiology, assessment, and treatment of these disorders.

Keywords Compulsive sexual behavior · Gender identity disorder · Paraphilias · Sexual dysfunction · Sexual health

1. Introduction

Sexual disorders in the *Diagnostic and Statistical Manual* (DSM-IV-TR) (1) are divided into three major categories:

1. Sexual dysfunctions, which are 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 regarding the associated disorders, course, familial patterns, and etiology. Before summarizing the criteria, prevalence, assessment, and treatment of the sexual disorders, we will present a brief discussion on the determinants of sexual health.

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 Robinson et al. (5) "sexual health is an approach to sexuality founded in accurate knowledge, personal awareness, and self-acceptance in which 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 regarding 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.

3. Sexual Dysfunction Disorders (Table 16.1)

3.1. Hypoactive Sexual Desire Disorder

According to the DSM-IV-TR, "The essential feature of hypoactive sexual desire disorder is a deficiency or absence of sexual fantasies and desire for sexual activity" (1; p.539). As

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TABLE 16.1. Categorization of sexual dysfunctions (1).

Sexual dysfunction	Diagnostic criteria
Hypoactive sexual desire disorder (302.71)	Persistently or recurrently deficient (or absent) sexual fantasies and desire for sexual activity. The judgement of deficiency or absence is made by the clinician, taking into account factors that affect sexual functioning, such as age and the context of the person's life.
Sexual aversion disorder (302.79)	Persistent or recurrent extreme aversion to, and avoidance of, all (or almost all) genital sexual contact with a sexual partner.
Female sexual arousal disorder (302.72)	Persistent or recurrent inability to attain, or to maintain until completion of the sexual activity, an adequate lubrication–swelling response of sexual excitement.
Male erectile disorder (302.72)	Persistent or recurrent inability to attain, or to maintain until completion of the sexual activity, an adequate erection.
Female orgasmic disorder (302.73)	Persistent or recurrent delay in, or absence of, orgasm following a normal sexual excitement phase. Women exhibit wide variability in the type or intensity of stimulation that triggers orgasm. The diagnosis of female orgasmic disorder should be based on the clinician's judgment that the woman's orgasmic capacity is less than would be reasonable for her age, sexual experience, and the adequacy of sexual stimulation she receives.
Male orgasmic disorder (302.74)	Persistent or recurrent delay in, or absence of, orgasm following a normal sexual excitement phase during sexual activity that the clinician, taking into account the person's age, judges to be adequate in focus, intensity, and duration.
Premature ejaculation (302.75)	Persistent or recurrent ejaculation with minimal sexual stimulation before, on, or shortly after penetration and before the person wishes it. The clinician must take into account factors that affect duration of the excitement phase, such as age, novelty of the sexual partner or situation, and recent frequency of sexual activity.
Dyspareunia (302.76)	Recurrent or persistent genital pain associated with sexual intercourse in either a man or woman.
Vaginismus (306.51)	Recurrent or persistent involuntary spasm of the musculature of the outer third of the vagina that interferes with sexual intercourse.

with all of the other sexual dysfunction disorders, the disturbance "must cause marked distress or interpersonal activity" and the dysfunction "is not better accounted for by another Axis I disorder or be due to physiologic effects of a substance or general medical condition." One of the complexities of making this diagnosis is that, according to the criteria, "The judgment of deficiency or absence is made by the clinician, taking into account factors that affect sexual functioning, such as age and context of the person's life" (1; p.541). 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-IV-TR (1; p.539) also emphasizes the importance of assessing the patient and partner for desire discrepancy because an apparent low desire in one partner may actually reflect the unusually high desire in the other partner. There is also a requirement to add three specifiers to the diagnosis. The clinician must judge whether the disorder is lifelong or acquired type, whether it is a generalized type and occurs in all instances, or whether it is a situational type that occurs intermittently, and finally, one must specify whether it is caused solely by psychological factors or by combined factors.

3.1.1. Prevalence

Most studies that have reported on rates of hypoactive sexual desire disorder (HSDD) in both men and women have found that the rates are higher in women (6). One study of individuals between the ages of 18 and 59 years reported that 33.4% of women and 15.8% of men report persistent low desire (7). In both women and men, the prevalence of HSDD increases with aging, particularly above the age of 60 years (8).

3.1.2. Etiology

Low desire can be caused by 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, gynecological disorders in women 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 (9). Other categories of medications that are particularly problematic are antihypertensives, including the beta-blockers and calcium channel blockers; intramuscular depo Provera used for birth control; and any medications that bind testosterone (10, 11).

Many psychosocial factors 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 (12). 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. In women, it is particularly difficult to differentiate physiologic arousal

disorders from desire disorders. However, 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.

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 exam should be done to exclude infection, poor or excessive hygiene, or other medical abnormalities as causes of the low desire. In postmenopausal women, vaginal atrophy can lead to discomfort during intercourse that can affect sexual desire. Laboratory studies should include thyroid function tests, because either hypothyroidism or hyperthyroidism can be associated with changes in sexual desire; hemoglobin and prolactin levels; and any other laboratory examinations as indicated by the history or physical exam (12). Estrogen levels in women are not particularly helpful, because levels vary over the course of the day and the menstrual cycle in normally menstruating women; during the perimenopausal period, estrogen levels vary even more widely (12). Although testosterone has sometimes been suggested as a treatment of low sexual desire in women, there are no lower limits of normal for testosterone in women, therefore, testosterone levels are not particularly valuable (13,14). Low testosterone in men may be a factor that contributes to low sexual desire (15), thus, obtaining a level in men can be useful.

3.1.4. Treatment

Although 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 affect 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 (12). Often, for these issues, couples or group psychotherapy is required. In group psychotherapy, single sex groups are the most common form of treatment (12). For women in particular, psychotherapeutic issues that must often be addressed are validation of the woman's feelings and experiences regarding her sexuality and an open discussion of sexuality to decrease the level of shame that is often associated with the sexual problem. Information regarding female sexual anatomy is crucial because some women do not have an understanding of the structure and function of female genitalia. For both men and women, sexual education regarding normal male and female 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 in women that have well-documented efficacy (15). There is much debate regarding whether oral contraceptives may decrease desire in women. If a patient has a history of low desire correlated with onset of use of contraceptives, then discontinuation with attention to another adequate form of birth control may be tried to see if this helps low desire. There is some evidence that triphasic oral contraceptives may improve desire (16). Exogenous progestins may increase libido; however, they may have a negative effect on mood and, thus, libido, as well as having a negative effect on lipid profile (17). Micronized progesterone may have fewer side effects than other formulations. Hormone replacement therapy may be useful in women who are postmenopausal; however, benefits of this treatment must be weighed against the known risks of hormone replacement treatment in postmenopausal women (18,19).

Testosterone supplementation may be effective particularly for women who have undergone surgical menopause (20). There is little evidence that the use of testosterone is effective in premenopausal women (10) and there is a risk of hypertension, acne, virilization, or accelerating atherosclerosis. Testosterone can be used to treat men with low desire who have low testosterone levels or low levels of bioavailable testosterone (21,22). Because of 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.

3.2. Female Sexual Arousal Disorder

3.2.1. Criteria and Prevalence

The DSM-IV-TR definition of female sexual arousal disorder is patterned after the male definition and, therefore, focuses on adequate lubrication–swelling response to sexual excitement (1; p.543). Approximately 16 to 21% of women report lack of lubrication and lack of sexual pleasure in large studies (23). Rates of lack of lubrication are higher in postmenopausal women, in whom 57% report difficulty (24). However, recent research demonstrates that arousal disorders in women may need to be defined more broadly than the current DSM-IV-TR definition that focuses on lubrication. Some women suffer from a lack of subjective arousal alone, whereas others suffer from both a lack of subjective arousal and a lack of genital congestion and lubrication (25). For instance, a large British

study of women 18 to 70 years old found that 17% of the women reported problems with arousal that was not associated with vaginal dryness (26). This was also true of 5% of the women in the SWAN study (27). 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.

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 (25). 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 (28). If there is sufficient stimulation, even women with estrogen deficiency may become adequately lubricated. However, in approximately 40% of women, vaginal atrophy does adversely affect sexual functioning and sexual response (29). There is a debate regarding the role of oral contraceptives in affecting sexual function. Oral contraceptives increase levels of sex binding globulin, which leads to reduced free testosterone levels, which could affect sexual function (30). There has been a lot of debate regarding the role of low testosterone in contributing to female sexual arousal disorder, and the use of testosterone in the treatment is controversial. However, no correlation has been found between sexual arousal and serum testosterone in large population studies of women (31). Multiple medical issues can contribute to arousal difficulties in women, including diseases such as multiple sclerosis, renal failure, and premature menopause by chemotherapy (25). Obviously, psychological and psychiatric problems can affect sexual functioning. Significant stress or discord with a partner can contribute to difficulties with arousal.

3.2.3. Diagnosis

A history; physical examination, including a gynecological exam; and laboratory testing need to be done to exclude medical illnesses that may be contributing to female 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, 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 (23).

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).

3.2.4. Treatment

There are two excellent recent reviews of treatment of arousal disorder in women by Basson (25) and Arlt (32). 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” (25). However, she does review the possible available therapies, including sildenafil, because of the involvement of nitric oxide in neurogenic vasodilation during sexual arousal in women (25). In a small trial of women with genital arousal disorder, some women reported improvement (33). However, in two larger trials in women with a combination of arousal and desire disorders, there was no improvement in desire, sensation, lubrication, or satisfaction (34). Sildenafil use is off-label in women and because 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 (25). The Women’s Health Initiative Trial raises important questions regarding 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 (32) 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 DHEA, DHEAS ... 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 (25) also agrees that a 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 nonpharmacologic agent that can be used to treat arousal disorder in women is the Eros-CTD (12). This is a US Food and Drug Administration (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 (12).

3.3. Male Erectile Disorder

The male version of sexual arousal disorder is officially titled male erectile disorder; however, the term erectile dysfunction is much more commonly used. According to the DSM-IV-TR, the definition of male erectile disorder is "persistent or recurrent to attain, or to maintain until the completion of sexual activity, an adequate erection."

3.3.1. Prevalence

According to a review by Beutel et al. (35), the prevalence of erectile dysfunction varies according to age. It is approximately 2.3% in 30- to 39-year-old men, and up to 5.9% in 40- to 49-year-old men. The reported range in 50- to 59-year-old men is from 2% up to 30.8%, depending on the series, and 11 to 55% for those over age 60 years. Reported prevalence for those older than age 70 years ranges from 15 to 53% and for men 80 years and older, 64 to 76%.

3.3.2. Etiology

Multiple medical problems can account for organic causes of erectile dysfunction, and these medical causes should be excluded 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 (35). 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.

3.3.3. Diagnostic Testing

The review article by Wespes et al. (36) summarizes the diagnostic testing for erectile dysfunction. The basic work-up for ED includes a detailed medical history that screens for all of the potential etiological factors described in the section above. The quality of the relationship with the partner and the quality of morning erections and erections during masturbation should also be explored. There are also several validated questionnaires that can be used to assess aspects of the problem, for instance the International Index for Erectile Function (128). A focused physical exam and laboratory tests as indicated by the history and physical should be pursued. In some cases referral to a specialist for further testing should be pursued. On such test, 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 test results.

Other vascular studies include intracavernous injection of a vasoactive drug to determine whether there is vascular insufficiency responsible for the erectile dysfunction (36). If the test is inconclusive, a duplex ultrasound of the penile arteries can be obtained. If the duplex examination result 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 (36).

3.3.4. Treatment

Treatment options fall into four basic categories (36). 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 three approved phosphodiesterase type 5 (PDE5) inhibitors (36, 129). Treatment with these medications causes increased arterial blood flow, leading to smooth muscle relaxation, vasodilation, and penile erection. Sildenafil, tadalafil, and vardenafil are the three 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 with 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 exclude 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 selective serotonin reuptake inhibitors (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 before 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 (36, 129). However, apomorphine may still be used in patients who take nitrates, because 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 (36). However, adverse events, such as skin and glans erythema, burning sensation, and allergic reactions can be associated with all of these and should be discussed carefully with the patient before administration. The partner can also experience hypotension and headache because of 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 base of the penis to retain blood within the copora (36, 129). 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 (36).

3.4. Female Orgasmic Disorder

Female orgasmic disorder is defined as "persistent or recurrent delay in, or absence of, orgasm, following a normal sexual excitement phase" (1; p.547). Again, 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.

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 (24). Single women seem to have a higher prevalence of the diagnosis compared with married or cohabitating women who are in a long-term committed relationship.

3.4.2. Assessment and Treatment

It is important, when treating female orgasmic disorder, to determine whether 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 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 (8,37,38). 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 regarding whether orgasm during intercourse without additional clitoral stimulation is a reasonable therapeutic goal for treatment of orgasmic disorder (37). 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 (8,39).

3.5. Male Orgasmic Disorder

According to the DSMIV-TR, the definition of male orgasmic disorder is "persistent or recurrent delay in or absence of orgasm following normal sexual excitement phase during sexual activity that the clinician, taking into account the person's age, judges to be adequate in focus, intensity, and duration" (1; p.545). The physician making this diagnosis needs to make sure they are adequately educated on norms of sexual function.

3.5.1. Prevalence

Male orgasmic disorder or delayed ejaculation was reported by 46.2% of men and increased with age from 30% for men aged 50 to 59 years to 54.9% in men aged 60 to 69 years,

and 74.3% in men aged 70 to 80 years (35). Inability to reach orgasm increased from 5% for 40- to 49-year-old men up to 17% for 70- to 80-year-old men in one study, but another reported less than 5% for men younger than age 60 years, 14% for men aged 60 to 69 years, 34% for 70- to 79-year-old men, and 55% for men older than 80 years (35).

3.5.2. Etiology

As with other types of sexual dysfunction, it is important to exclude potential medical causes of delayed ejaculation. Potential causes and treatments are reviewed by Richardson et al. (40). 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 SSRIs, tricyclic antidepressants, and antipsychotic medications.

3.5.3. Treatment

Most of the publications regarding use of medications to treat delayed ejaculation are related to management of the problem when it is secondary to the use of serotonin reuptake inhibitors (40). Amantadine, cycloheptadine, and yohimbine have all been suggested for treating delayed ejaculation caused by SSRIs. There have been some single-blind and double-blind studies of bupropion to treat SSRI-induced sexual dysfunction (41). Results have been mixed, but bupropion is often tried in clinical practice. Bethanechol has been reported to be effective in treating delayed ejaculation caused by tricyclic antidepressants (42), 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 (43–45).

Recommendations by sex therapists to treat delayed 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 before intercourse (40). Hypnosis has been suggested as a useful adjunct to treatment (40).

3.6. Premature Ejaculation

3.6.1. Prevalence

In the review by Beutel et al. (35), 14% of men reported periodic to frequent early 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 aged 40 to 59 years, and 17 to 18% in men aged 60 to 80 years.

3.6.2. Treatment

Pharmacotherapy for premature ejaculation most commonly takes advantage of the side effects of the SSRIs. 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 [46]). There are also reports of topical anesthetics, such as lidocaine and prilocaine preparations, and PDE5 inhibitors being used to treat premature ejaculation (reviewed in [46]). 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 (46).

3.7. Dyspareunia

3.7.1. Definition and Prevalence

Dyspareunia, defined as pain during intercourse, can occur in either men or women. The estimated prevalence in men is approximately 1 to 1.5% (reviewed in (8)). In contrast, approximately 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 (6, 8)). 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 (24).

3.7.2. Etiology

Physical factors that can cause dyspareunia in women include hymeneal scarring, pelvic inflammatory disease, and vulvar vestibulitis (8). 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 (6). Psychological factors, such as problems in the relationship with one's partner or a history of sexual abuse, can also contribute to dyspareunia. As with other sexual dysfunction disorders, the organic cause of the original pain may not be the only factor for maintaining the problem and, therefore, an approach that examines both the physical and psychological aspects of the disorder are important.

3.7.3. Treatment

Various medical and surgical procedures for dyspareunia can address the various organic causes of this disorder. However, because, in many cases, there has been a long history of dyspareunia before medical or surgical intervention, there is often much residual anxiety and often decreased arousal in women with dyspareunia (8). Cognitive–behavioral therapy and sex therapy treatment have both been used to treat dyspareunia.

3.8. Vaginismus

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 (6,8). One of the questions regarding diagnosis of vaginismus is how to distinguish it from dyspareunia. Often it is difficult to determine whether 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 (47).

3.8.2. Treatment

Physical treatment for vaginismus includes use of vaginal dilators. The 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 (8). As with most cases of sexual dysfunction, treatment seems to be more effective if both partners participate and are invested in treating the condition.

3.9. Sexual Aversion Disorder

3.9.1. Definition and Clinical Characteristics

Sexual aversion is defined as "extreme aversion to and avoidance of, all (or almost all) genital sexual contact with a sexual partner" (1). Compared with the literature on HSDD 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 healthcare professionals (48). 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 do not 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 (48). Interestingly, approximately half of the women with sexual aversion have normal desire. They may masturbate regularly and they may have average levels of sexual fantasy (48). There are no studies documenting the efficacy of treatment, but individual or couples therapy is usually the recommended treatment, although women may not tolerate the traditional sex therapy approaches.

4. Gender Identity Disorder

The DSM-IV-TR criteria for gender identity disorder in children, adolescence and adulthood are listed below in Table 16.2 (1; p.581). For persons who do not meet the full criteria there is a Not Otherwise Specified category. With the publication of the DSM-IV-TR, the diagnosis of Transsexualism was replaced with Gender Identity Disorder. The *International Classification of Diseases*, 10th edition (ICD-10) still retains

TABLE 16.2. Categorization of gender identity disorders.

Gender identity disorder	Diagnostic criteria
Gender identity disorder (302.6)	A strong and persistent cross-gender identification (not merely a desire for any perceived cultural advantages of being the other sex). In children, the disturbance is manifested by four (or more) of the following: 1) repeatedly stated desire to be, or insistence that he or she is, the other sex; 2) in boys, preference for cross-dressing or simulating female attire; in girls, insistence on wearing only stereotypical masculine clothing; 3) strong and persistent preferences for cross-sex roles in make-believe play or persistent fantasies of being the other sex; 4) intense desire to participate in the stereotypical games and pastimes of the other sex; 5) strong preference for playmates of the other sex. In adolescents and adults, the disturbance is manifested by symptoms such as a stated desire to be the other sex, frequent passing as the other sex, desire to live or be treated as the other sex, or the conviction that he or she has the typical feelings and reactions of the other sex. Persistent discomfort with his or her sex or sense of inappropriateness in the gender role of that sex. In children, the disturbance is manifested by any of the following: in boys, assertion that his penis or testes are disgusting or will disappear or assertion that it would be better not to have a penis, or aversion toward rough-and-tumble play and rejection of male stereotypical toys, games, and activities; in girls, rejection of urinating in a sitting position, assertion that she has or will grow a penis, or assertion that she does not want to grow breasts or menstruate, or marked aversion toward normative feminine clothing. In adolescents and adults, the disturbance is manifested by symptoms such as preoccupation with getting rid of primary and secondary sex characteristics (e.g., request for hormones, surgery, or other procedures to physically alter sexual characteristics to simulate the other sex) or belief that he or she was born the wrong sex.

Transsexualism as a diagnosis for adults, but also includes dual-role transvestism, gender identity disorder of childhood, other gender identity disorder, and gender identity disorder unspecified.

There is significant debate in the transgendered community and among practitioners who provide services for transgendered individuals regarding whether gender identity disorders are mental disorders. Those arguing against having gender identity disorder in the DSM posit that it adds to social stigmatization of a normal variant of human gender expression. Others feel very strongly that it is only because of the formal diagnosis that those with gender identity 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 identity disorders developed by the Harry Benjamin International Gender Dysphoria Association (49). These guidelines provide standards for assessment and treatment of gender identity disorder in children, adolescents, and adults, and these guidelines are used as the basis of the discussion that follows.

4.1. Prevalence

It is estimated that approximately 1 in 11,900 male patients and 1 in 30,400 female patients would be eligible for the diagnosis of gender identity disorder (49). However, the prevalence may be even higher because the social stigma associated with the condition could certainly provide an underestimate of the prevalence of the disorder. Additionally, in some patients, the intensity of the gender identity disorder 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 homosexual individuals have a form of gender identity disorder (49, p.2).

Little is known regarding the course of gender identity disorder 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 (49). 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 (50).

4.2. Clinical Presentation

It is important to note that the majority of children who present with gender identity disorder do not go on to be transgendered adults (49). 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 identity disorder do not become transsexual, although research indicates that they may eventually become homosexual (49; pp.8,9). Gender identity disorder in boys is more closely tied to later homosexuality than to the development of adult transsexualism. Retrospective studies of male and female homosexual individuals are more likely to endorse cross-dressing in childhood and adolescence than in heterosexual individuals.

Often, when adult transsexual individuals 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 to have surgery immediately. They often exhibit a great deal of distress regarding 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 to not have the cross-dressing apparent to others. They may have already selected a name of the desired gender and are very anxious to proceed with the sex change.

4.3. Assessment

When seeing a patient with gender identity disorder, 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, one can be found in the Harry Benjamin International Gender Dysphoria Association Standards of Care (49). Irreversible interventions, including any surgical intervention, should not be carried out before adulthood.

Differential diagnosis of gender identity disorder in adults is most difficult when distinguishing from transvestic fetishism and gender identity disorder, particularly if the patient presents stating that the cross-dressing is sexually arousing. Additionally, young male homosexual individuals with a history of stereotypically feminine interests or behaviors and possibly cross-dressing may be mistaken for patients with gender identity disorder.

4.4. Treatment

According to the Standards of Care, there are five elements to the clinical work of professionals with patients with

gender identity disorder. They include diagnostic assessment, psychotherapy, real-life experience, hormone therapy, and surgical therapy. Psychiatrists who work with patients with gender identity disorder may appropriately carry out any of the following responsibilities (49):

1. Accurately diagnose the individual's gender disorder.
2. Accurately diagnose comorbid psychiatric conditions and appropriate treatment of such conditions.
3. Counsel individuals regarding 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 identity.
9. Educate family members, employers, and institutions regarding gender identity disorders.
10. Be available for follow-up of patients who receive treatment of gender identity disorder.

Patients with gender identity disorder may select from a whole range of options to deal with their disorder. Although some are comfortable with finding a middle ground, taking hormones but not having surgery, or, in the case of women, having a 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 (49). This involves dressing, presenting, and living as an individual of the gender of choice for a period of time before 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 before irreversible physical changes are 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.

4.5. Hormone Therapy

Hormones should only be prescribed by a practitioner who is fully versed in the potential medical consequences and attends to the management of these consequences, such as changes in glucose tolerance and possible development of diabetes, effects on cardiovascular disease, venous thromboembolitic disease, liver abnormalities, hyperprolactinemia, and osteoporosis. Programs following the Standards of Care make certain that the person receiving hormones be at least 18 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 (49). The medical and social risks should not be minimized. The person must also either have a documented real-life experience in the gender of choice of at least 3 months before 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 3 months) (49).

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 identity disorder (49). Eligibility for a surgical sex reassignment includes being of the legal age of majority, having 12 months of continuous hormone therapy, and 12 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 for 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. Patients 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. Although 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 (49).

5. Paraphilias and Compulsive Sexual Behavior

5.1. Paraphilias

The DSM-IV-TR describes paraphilias as sexual disorders characterized by recurrent, intense, sexually arousing fantasies, urges, or behaviors that involve nonhuman objects, children, other nonconsenting individuals, or the suffering or humiliation of the individual or partner (1). DSM-IV-TR recognizes eight specific paraphilias (Table 16.3) and a category of paraphilias not otherwise specified, which may include telephone scatologia (obscene phone calls), necrophilia (corpses), partialism (exclusive focus on a body part), zoophilia (animals), coprophilia (feces), klismaphilia (enemas), and urophilia (urine) (1). The diagnosis of a paraphilia requires that the symptoms have existed for at least 6 months. For the diagnosis of pedophilia, voyeurism, exhibitionism, sexual sadism, and frotteurism, the person must have either acted on these urges or the urges or fantasies have caused significant impairment in functioning or distress.

Although often discussed in a group, there is considerable debate regarding which of the paraphilias, if any, share a common underlying etiology. In addition, there is also debate regarding whether certain paraphilias (e.g., sexual sadism, sexual masochism, pedophilia) should even be considered psychiatric disorders (51,52).

5.1.1. Prevalence

There have been no large epidemiological studies of paraphilias, and, thus, the rates in the general community are not known. Small nonclinical studies, however, suggest that paraphilias 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 (53). In a different study of male college students, 3% reported having been sexual with a girl younger than the age of 12 years, 42% had been voyeurs, 2% had exposed themselves, and 35% had engaged in frotteurism (54).

5.1.2. Clinical Characteristics

Paraphilias seem to start by late adolescence, except pedophilia, which has a mean age of onset in the mid or late 20s (55). Although paraphilias, for most individuals, begin by young adulthood, they may in fact start at any age (56). 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 (57).

Paraphilias, although present in women (58, 59), seem to be more common in men (57). Given the paucity of research on women with paraphilias, it is still unclear whether gender influences the clinical characteristics of these disorders.

Co-occurring disorders are common in individuals with paraphilias, 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 paraphilias (51,56,60,61). Additionally, individuals with paraphilias tend to have multiple paraphilias (56, 61–64).

5.1.3. Etiology

Although the biology of sexual functioning and hypersexuality has long been explored (65–67), 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 disorder seem to have high rates of exhibitionism (68), these circuits may be a particularly important area for research. Pedophilia has been associated with a case of

TABLE 16.3. Paraphilias.

	During a period of at least 6 months, recurrent, intense sexually arousing fantasies, sexual urges, or behaviors involving:
Exhibitionism (302.4)	The exposure of one's genitals to an unsuspecting stranger
Fetishism (302.81)	The use of nonliving objects (e.g., female undergarments)
Frotteurism (302.89)	Touching and rubbing against a nonconsenting person
Pedophilia (302.2)	Sexual activity with a prepubescent child or children (generally age 13 years or younger)
Sexual masochism (302.83)	The act (real, not simulated) of being humiliated, beaten, bound, or otherwise made to suffer
Sexual sadism (302.84)	Acts (real, not simulated) in which the psychological or physical suffering (including humiliation) of the victim is sexually exciting to the person
Transvestic fetishism (302.3)	Cross-dressing (in a heterosexual male)
Voyeurism (302.82)	The act of observing an unsuspecting person who is naked, in the process of disrobing, or engaging in sexual activity

an orbitofrontal tumor, which resolved once the tumor was removed (69). A neuropsychological study of four individuals with pedophilia suggests that a striato–thalamo–cortical circuit may be involved in the pathophysiology of some cases of pedophilia (70).

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 (71, 72). 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 (65). 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 non-offenders (73).

Animal models may hold some answers to etiology because pedophilia and exhibitionism have been reported in many species (74). 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 (73).

Multiple psychological models have also been proposed for the possible etiology of paraphilias. Behavioral models hypothesize that early conditioning to sexually deviant behavior results in the development of a paraphilia (75). Social learning models suggest that lack of parental care, physical punishment, and frequent sexual activity within the family may predispose children to offending (76). Additionally, an addiction model has hypothesized that deviant sexual behavior acts as a drug substitute (73). 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 paraphilias, 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 paraphilias, 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.

5.1.4. Treatment

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 has demonstrated efficacy in reducing recidivism (77–79). Studies assessing this treatment approach, however, have generally focused on sex offenders, regardless of specific paraphilia, have included short treatment durations, and the studies have failed to use a no-treatment control group for comparison.

5.1.4.2. Pharmacotherapy

Although no consistent findings regarding testosterone levels among individuals with paraphilias 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 (80). Although promising in case reports and case series (78), there have been no double-blind controlled studies examining their efficacy. Similarly, case reports suggest that synthetic analogs 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 (81–83).

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 (84, 85), fetishism (85), sexual masochism (85), transvestic fetishism (85), and voyeurism (86). There is, to date, no evidence that SSRIs differ in efficacy. No double-blind trials of SSRI medications have been conducted in individuals with paraphilias. When using these medications, one has to be particularly careful regarding the anorgasmia or delayed orgasm side effect, because 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.

5.2. Compulsive Sexual Behavior (Sexual Disorder Not Otherwise Specified)

As with all of the other sections of the DSM-IV-TR, there is a “not otherwise specified” category at the end of the sexual disorders chapter. One of the important conditions that is frequently diagnosed in this category goes by a variety of names. These include 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 (87–89, 98). Salient features include recurrent and intense normophilic (as opposed to paraphilic) sexually arousing fantasies, sexual urges and behaviors that cause clinically significant distress in social, occupational, or other important areas of functioning. The hypersexuality must not be caused by other medical conditions or substance use disorder, must not be attributable to another Axis I disorder or developmental disorder, and must take into account norms of gender, sexual orientation, and sociocultural groups (88). Numerous behaviors have been described of those exhibiting CSB, including compulsive cruising, multiple partners, compulsive masturbation, compulsive sexuality in a relationship, pornography dependence, telephone sex dependence, and cybersex dependence (88, 90).

Hyperactive sexual desire or hypersexual behavior is related to CSB. Data published by Kafka (90, 91) 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. TSO 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 men is 0.5 to 3 times per week, and, in all of the studies, a TSO of 7 or greater seems to be in the upper 3 to 8% of men (7, 92, 93). Kafka (94) demonstrated that patients with CSB and those with paraphilias both exhibit hypersexual behavior at the same rates. In a sample of 206 men 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. Reports indicate that men spend an average of 1 to 2 hours a day engaged in compulsive behaviors (94, 95). The primary sexual outlet was masturbation.

5.2.1. Prevalence

There are no epidemiologic studies of the prevalence of CSB. However, Grant et al. (96) reported that 6.5% of 204 consecutive patients admitted to two inpatient psychiatry wards met criteria for CSB on a structured interview administered with the Structured Clinical Interview for DSM-IV. Others have estimated the prevalence to be approximately 5% (97). 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 men (Raymond NC, Lloyd MD, Coleman E, unpublished clinical data; (87, 95, 99)). Patients tend to present for treatment in their late 30s to early 40s 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 (Raymond NC, Lloyd MD, Coleman E, unpublished clinical data; (87, 95, 99)). 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.

5.2.2. Etiology

There are many theories regarding the etiology of CSB, but no substantive research in the area. There are those who see the behavior as similar to addictive behavior and posit that the mechanism of drug and sexual addiction are similar (100, 101). Others see the disorders as being a type of paraphilia and assume that the etiology, although unknown, is similar to that of the paraphilias (100). To the extent that CSB is related to paraphilias, the discussion above in Sect. 5.1.3 regarding the etiology of the paraphilias can also apply to CSB. Others see CSB as a way to cope with anxiety and/or dysphoric mood (97, 101). Impulsivity (102) and hypersexuality (103) 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 CSB is similar to the abnormalities that lead to pathological gambling and other impulse control disorders (104, 105). There are multiple case reports in the literature of individuals with head injuries who develop hypersexual behavior. The majority of these lesions are in the frontal and temporal lobes (67, 106–109).

5.2.3. Treatment

There is only one published placebo-controlled trial of citalopram for the treatment of CSB (110). Treatment with citalopram leads to decreases in sexual desire/drive, frequency of masturbation, and use of pornography (110). 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 that SSRIs such as fluoxetine, sertraline, and paroxetine can decrease CSB (85, 86, 111–119). The SSRI may work by decreasing urges to engage in the behavior and decreasing preoccupation. There are also case reports of tricyclic antidepressants (120) and buspirone (121, 122) being effective to help decrease anxiety and frequency of problematic behavior in those with CSB. Nefazodone has been recommended as an alternative to SSRIs because it is not as likely to cause sexual dysfunction (123), but the recent "black box" warnings regarding liver dysfunction have decreased the use of this medication. Earlier case reports indicate that lithium carbonate and carbamazepine may be helpful in treating CSB (112,124,125). Atypical antipsychotic agents have been suggested as an option (111), particularly

in those with any Axis I or II psychotic symptoms in addition to their CSB. More recently, naltrexone has been recommended for the treatment of behavioral addiction, including CSB (104, 105, 126). High doses of 100 to 150 mg are generally needed. The use of nonsteroidal anti-inflammatory drugs is contraindicated with high-dose naltrexone, and liver functions must be followed carefully (127).

5.3. Conclusions

Paraphilias and CSB 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 paraphilias 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 seem 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 cognitive–behavioral therapy cannot be sufficiently addressed with the available data.

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17
Other Psychiatric Syndromes: Adjustment Disorder, Factitious Disorder, Illicit Steroid Abuse, and Cultural Syndromes

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Abstract Standard psychiatric textbooks frequently omit less common but important clinical topics related to a medical model view of psychiatry. This chapter covers four such additional topics: adjustment disorder, factitious disorder, psychiatric effects of illicit anabolic steroid abuse, and special psychiatric syndromes identified by eponyms or cultural ties.

Keywords Adjustment disorder · Anabolic steroid abuse · Factitious disorder · Cultural syndromes

Adjustment disorder and factitious disorder are psychiatric syndromes important in the medical setting. Adjustment disorder occurs commonly in the medically ill patient presenting for psychiatric consultation. Patients with factitious disorder, although rare, present a challenge for medical personnel in assessment and management. The psychiatric aspect of anabolic steroid use is an emerging area of study and clinical relevance. Most understanding of the psychiatric effects of illicit steroid use has occurred recently. Finally, psychiatric eponyms and cultural syndromes describe unique clinical profiles and provide a method to classify certain clinical presentations. A glossary of these eponyms increases awareness of the history of psychiatric classification. Culture-bound syndromes highlight the role of environment and society in the presentation of psychiatric disorders.

1. Adjustment Disorder

1.1. Definition

Adjustment disorder constitutes a group of disorders defined by a maladaptive response to a stressor. The *Diagnostic and Statistical Manual*, 4th edition, text revision (DSM-IV-TR) criteria for adjustment disorder includes:

- The development of emotional or behavioral symptoms in response to an identifiable stressor(s) occurring within 3 months of the onset of the stressor(s).
- These symptoms or behaviors are clinically significant as evidenced by either of the following: marked distress that is in excess of what would be expected from exposure to the stressor and significant impairment in social or occupational (academic) functioning.
- The stress-related disturbance does not meet the criteria for another specific Axis I disorder and is not merely an exacerbation of a preexisting Axis I or Axis II disorder.
- The symptoms do not represent bereavement.
- Once the stressor (or its consequences) has terminated, the symptoms do not persist for more than an additional 6 months.

Adjustment disorders are subclassified according to the dominant clinical symptoms. Table 17.1 defines the categories of adjustment disorder according to DSM-IV-TR (1).

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 longer than 6 months. The disorder is transient, with resolution over time or with development into a more severe syndrome, such as major depressive disorder.

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 after 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 1V.

From: S. H. Fatemi and P. J. Clayton (eds.): *The Medical Basis of Psychiatry*

TABLE 17.1. Classification of adjustment disorders

309.0	Adjustment disorder with depressed mood
309.24	With anxiety
309.39	With mixed anxiety and depressed mood
309.3	With disturbance of conduct
309.4	With mixed disturbance of emotions and conduct
309.9	Unspecified

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 (2–10). These studies suggest that adjustment disorder is a frequent clinical condition worthy of further study. Several prevalence studies of adjustment disorder are noted in Table 17.2.

1.3. Clinical Picture

The clinical profile of symptoms in adjustment disorder is very variable and seem dependent on the age of the individual. Adolescents seem to be more likely to develop behavioral problems with acting-out symptoms. Adults seem 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).

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 that 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 regarding 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, 5 mg warfarin daily, sublingual nitroglycerin, 40 mg furosemide daily, 37.5 mg captopril three times daily, 0.125 mg digoxin daily, 10 mg metoclopramide four times daily, and 5 mg diazepam every 6 hours as needed. Mrs. K reported that the diazepam relieved her anxiety symptoms, but she had received only one dose during the last 72 hours. The 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 study results. Complete blood count, arterial blood gases, and general chemistry screen results 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

TABLE 17.2. Prevalence estimates of adjustment disorder in various populations.

Category	n	Site	Contact	Prevalence (%)	Author, year (reference)
Children	386	Community	Survey	4.2–7.6	Bird et al., 1988 (2)
Adolescent suicides	56	Urban	Postmortem	14	Runeson, 1989 (3)
Suicide attempters	127	Inpatient	Consult	24.4	Hale et al., 1990 (4)
Gunshot wounds	260	Inpatient	Consult	10	Frierson et al, 1990 (5)
Consultation series	1048	Inpatient/outpatient	Consult	11.5	Popkin et al., 1990 (6)
Geriatric	197	Nursing home	Consult	16	Loebel et al., 1991 (7)
Psychiatric clinic	5573	Outpatient	Diagnostics	12.3	Fabrega et al., 1987 (8)
Psychiatric hospital	2699	Inpatient	Admissions	5	Andreasen et al., 1980 (9)
Bone marrow transplantation	95	Outpatient	Survey	34.7	Kirsh et al., 2004 (10)

with anxious mood was diagnosed after excluding the other diagnostic considerations. Recommendations included a trial of 5 mg diazepam twice daily and an additional 5 mg as needed during hospitalization. Continued diazepam treatment after discharge was thought 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.

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 more than 70% without significant impairment or psychiatric illness 5 years after the index diagnosis (9). 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 a 4% suicide rate in this study population. Patients admitted to a psychiatric hospital with a diagnosis of adjustment disorder with depressed mood seem 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 (11).

The prognosis of adjustment disorder seems less optimistic in the adolescent population. Andreasen and Hoerick's study (12) 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 with other mood disorders (13).

One study of youths with new-onset insulin-dependent diabetes mellitus found a high rate of new psychiatric disorders in a 5-year follow-up (14). Forty-eight percent of those with adjustment disorder subjects had a new psychiatric illness diagnosed compared with only a 16% rate in control subjects.

Masterson (15) 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 seems to be especially poor if there is a disturbance of conduct (16). Psychiatric comorbidity may significantly contribute to poor prognosis in children with adjustment disorder (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 very 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 (12). 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 seems also to play a role in the etiology of adjustment disorder. The risk of developing psychiatric symptoms seems to increase with increased stressor severity. However, the response does need to meet the maladaptive and excessive response 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 (18).

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 before a surgical procedure would include adjustment disorder with anxious mood, generalized anxiety, panic disorder, simple phobia, anxiety caused by 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-IV is the category of psychological factors affecting physical condition. In this disorder, the focus of attention is worsening of a

physical condition caused by 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 after the death of a relative exemplifies psychological factors affecting physical condition.

A final stress-related category in DSM-IV 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 reexperienced, 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 major depression, dysthymia, panic disorder, and generalized anxiety disorder in patients seen for conditions in which adjustment disorder is being considered. Clinical factors seem to distinguish adjustment disorder with depressed mood from major depression (19). In a general hospital psychiatry series, major depression was linked to older age, widowed marital status, and living alone (20). Psychosocial stressors can exacerbate nearly any chronic psychiatric disorder, and the resultant increase in symptoms may seem to be caused by 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.

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 very 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 after exposure to significant military stressors (21). This model uses a brief intervention approach beginning as soon as possible after 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—brief intervention strategies follow 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.

Medication approaches for adjustment disorder target the primary presenting complaint (22). The majority of adjustment disorder diagnoses are subclassified 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 (23). Patients in primary care suffering from adjustment disorders seem to respond well to antidepressant therapy (24). However, large placebo-controlled studies of the efficacy of antidepressant treatment in adjustment disorder are generally lacking.

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 regarding 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 0.75 to 3 mg alprazolam in three divided doses, 1.5 to 6 mg lorazepam in three divided doses, 0.5 to 1 mg clonazepam in two divided doses, or 10 to 30 mg diazepam in a single or a 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 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.

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 regarding 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.

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-IV (1) criteria for factitious disorder includes:

- Intentional production or feigning of physical or psychological signs or symptoms
- The motivation for the behavior is to assume the sick role
- External incentives for the behavior (such as economic gain, avoiding legal responsibility, or improving physical well-being, as in malingering) are absent

This 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 healthcare team. The management of factitious disorder also adds to the challenging character of these disorders.

2.1. Definition

DSM-IV-TR defines three categories of factitious disorder. The first category is factitious disorder with predominantly physical signs and symptoms. This is the category that covers the earliest described factitious disorder—Münchhausen syndrome (25) The essential features of Münchhausen 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-IV-TR 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. A residual diagnostic category is factitious disorder with combined psychological and physical signs and symptoms. 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 (26). A form of factitious disorder in childhood exists. Referred to as Münchhausen 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 (27).

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 17.3 notes the prevalence findings for factitious disorder in the medical setting.

2.3. Clinical Picture

The presenting clinical sign or symptom for factitious disorder can be very 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 hypoglycemia in diabetic patients 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

TABLE 17.3. Prevalence of factitious disorder in treatment populations.

Category	n	Site	Contact	Prevalence (%)	Author, year (reference)
Teaching hospital	1361	Inpatient	Consult	1	Sutherland et al., 1990 (33)
Fever of unknown origin	343	Inpatient	Referral	9.3	Aduan et al., 1979 (34)
Psychotic disorder	219	Inpatient	Series	4.2	Pope et al., 1982 (29)

have developed (28). Feigned psychosis and feigned PTSDs exemplify factitious disorder with psychological symptoms (29,30).

In Münchhausen syndrome by proxy, several similarities exist compared with adult factitious disorder (27). 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.

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 during 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 before 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 a blood transfusion to correct the anemia.

Ms. L denied any significant psychological distress. She did not seem depressed or anxious or have any psychotic symptoms. She did not respond to the intermittent swelling with anxiety or increased concern regarding 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 of the patient's high school homework and paper assignments. After 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.

2.5. Clinical Course

Separating factitious disorder into those with a Münchhausen syndrome and those without defines two different prognostic groups. Münchhausen syndrome has a very poor prognosis, with only one case report of successful treatment (31). Factitious disorder without a Münchhausen syndrome seems 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 (32). After 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 because of self-induced hypoglycemia.

The outcome of factitious disorder with psychological symptoms has received limited attention. In the study by Pope et al. (29) 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 (27). 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.

2.6. Etiology

The etiology of factitious disorder is unknown. 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 seems 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 healthcare team and getting revenge for previous interpersonal conflicts.

The common finding of a medical background in factitious disorder suggests that medical knowledge facilitates the disorder in patients who have vulnerable personality structures.

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. Nonmonetary secondary gain also can be the motive for malingering. Nonmonetary 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 healthcare 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 (33).

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, whereas 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 caused by 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. Management of the syndrome can be as complicated as the diagnostic process.

2.8. Laboratory Tests

Laboratory tests can occasionally provide supporting evidence for the diagnosis of factitious disorder. 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 (32). 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 (34). 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.

2.9. Treatment

The treatment of factitious disorder involves a coordinated medical and psychiatric assessment and treatment plan (35). 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 that the self-injurious behavior has occurred 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 nonpunitive fashion follows. This example is taken as a hypothetical approach to the illustrative case before 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 that 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 their individual psychiatric presentation. For patients with concurrent borderline personality disorder, cognitive therapy strategies for personality disorders exist (36). 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 Münchhausen 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.

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 seems 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 is examined.

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 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 regarding the epidemiology of AS use (36). Table 17.4 summarizes several of the surveys with the best methodologies (37–42).

Yesalis (43) argues that survey methods probably underestimate the prevalence rates of AS use. Nonresponse bias is likely to play a role in underestimation because of 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 (43). 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.

Several risk factors seem related to AS use. Male sex predominates in this problem. Specific sports and specific positions within sports have higher rates of AS use. The rank

TABLE 17.4. Prevalence rates of AS use in various populations

Category	n	Period	Males (%)	Females (%)	Author, year (reference)
High school students (12th grade)	2, 350	Lifetime	5.0	0.5	Johnston et al., 1990–1991 (37)
High school students (12th grade)	3, 403	Lifetime	6.6	N/A	Buckley et al., 1988 (38)
College athletes	12	months	6.2	0.6	Anderson et al., 1991 (39)
Elite power lifters	45	Lifetime	55	N/A	Yesalis et al., 1988 (40)
Elite multiple-sport athletes	271	Lifetime	N/A	2	Newman, 1987 (41)
NCAA athlete survey	637	12 months	1.1%[a]		Green et al., 2001 (42)

[a]Survey reported both genders combined. N/A, not applicable.

order of AS use among Division I National Collegiate Athletic Association male athletes is as follows: 1) football; 2) baseball; 3) track/field; 4) basketball; and 5) tennis (39).

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 (44). Typically, the AS use pattern involves the use of multiple compounds. Compounds can include oral as well as injectable drugs. Although AS were used for therapeutic indications for many years, illicit users typically use 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.

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 (45). These studies tended to be small and uncontrolled. AS treatment studies for depression decreased after 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 (46, 47). Some individuals using high doses experience minimal psychiatric effects, whereas 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 are being used, a feeling of enhanced self-esteem and euphoria with increased energy and other mania-like features has been described (48). Depressive symptoms have been reported during on and off-cycle periods of use. Case reports of suicide in AS users also have been published (49, 50). The frequency that these mood syndromes meet criteria for a psychiatric diagnosis is unclear. Pope and Katz (51) argue for full affective syndromes in up to 12% of users, whereas other studies suggest that although psychiatric symptoms are common, the production of a syndrome characteristic of a full psychiatric disorder is rare (52, 53).

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 seem to be most likely to induce psychotic symptoms. Compounds in this class include oxandrolone, methandrostenolone, and oxymetholone. 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 that is 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 (54). Animal studies report that the aggressive effects of testosterone seem 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 seem important in determining the pattern and severity of response in males exposed to exogenous AS. Rejeski et al. (55) 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 because there is some indication that AS users are more likely to have premorbid antisocial personality disorder (56).

The study of the aggressive effects of AS 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. (57) examined the role of AS use in a group of AS users and controls using the Buss–Durkee Hostility Inventory (BDHI) (58). 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 control subjects (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 (59, 60). 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 (61, 62). 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 (57). Interestingly, a subject in the Su et al. study (62) asked to be placed in seclusion to prevent aggressive behaviors from getting out of control and resulting in harm to others.

Significant questions regarding 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 seem 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 seems common, the majority of users have subclinical mental status effects. Despite this, documented significant clinical mental status and behavioral effects of AS use do seem 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.

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 regarding our understanding and treatment of AS use.

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 US 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 (63) 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 are reviewed.

Support for the addiction hypothesis of AS 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 17.5

TABLE 17.5. Comparison of use of AS compounds with alcoholism and cocaine abuse phenomenology

Comparison categories	Alcoholism	Cocaine abuse	AS use
Male sex 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	?
Controlled Substance Act	No	Yes	Yes
Family history of abuse	Yes	Yes	?
Used primarily for psychoactive effect	Yes	Yes	No
Seek treatment for discontinuation	Yes	Yes	?/No
Biologic mechanism/drug causes "high"	Yes	Yes	?
Withdrawal symptoms/craving	Yes	Yes	?
Animal model for self-administration	Yes	Yes	Yes

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 sex phenomenon. Although found in women, the male to female ratio for AS use seems to be approximately 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 to female ratio for alcohol abuse and dependence is 6:1, and for non-alcohol abuse and dependence is 1.6:1 (64). The age of onset for AS use is adolescence and early adulthood; this also 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 (56).

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. According to DSM-IV criteria for psychoactive substance dependence, at least three of seven criteria are necessary for diagnosis of a dependence syndrome.

Brower et al. (65) 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 of 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

TABLE 17.6. Psychiatric syndromes identified with eponyms.

Eponym	Description	Found in	Author, date (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	Capgras et al., 1923 (68)
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 caused by a general medical condition	Clerambault, 1942 (69)
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 caused by a mood disorder or a general medical condition	Cotard, 1882 (70)
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	Trethowan, 1965 (71)
DaCosta's Syndrome	The syndrome, also known as neurocirculatory asthenia, characterized by easy fatigability, chest pain, dyspnea, and palpitations	Many cases probably panic disorder	Da Costa, 1871 (72)
Fregoli's delusion	The reverse of Capgras delusion; strangers are identified as familiar friends or family members	Schizophrenia, psychosis caused by a mood disorder, dementia	Courbon and Fail, 1927 (73)
Ganser's syndrome	A syndrome in which responses to questions are approximate but not correct; also described as hysterical pseudodementia	Schizophrenia, bipolar disorder, psychosis caused by a mood disorder, malingering	Ganser, 1898 (74)
Kleine–Levin Syndrome	Periodic episodes of hypersomnia accompanied by bulimia	Thalamic lesions	Carpenter et al., 1982 (75)
Kluver–Bucy	The loss of facial recognition, rage reactions, hypersexuality, and memory deficits	Surgical removal of both temporal lobes	Cummings and Duchen, 1981 (76)
Othello's delusion	The delusion of infidelity by the spouse	Paranoid disorder, Schizophrenia, psychosis caused by a mood disorder or a general medical condition, alcohol dependence	Enoch and Trethowan, 1979 (77)

TABLE 17.7. Cultural psychiatric syndromes.

Cultural syndrome	Description	Culture	Author, date (reference)
Amok	Unexpected rapid development of agitation; accompanied by obtaining a weapon and attacking everything in sight until apprehended	Malaysia	Westermeyer, 1972 (78)
Dhat	Delusion that sperm is leaking from the body through urination, resulting in weakness	India	Carstairs, 1956 (79)
Koro	An acute anxiety state characterized by fear that the penis will retract into the abdomen, resulting in death	China and Malaysia	Arieti and Meth, 1959 (80)
Latah	A syndrome of echopraxia, echolalia, and coprolalia; behaviors may involve putting oneself in dangerous situations	Malaysia;described in Africa, Japan, and Russia	Yap, 1952 (81)
Piblokto	Attacks of bizarre behavior, including screaming, running about, and tearing off clothing	Eskimo	Ackerknecht, 1948 (82)
Voodoo	A delusion of possession by devils or evil spirits	Haiti and Africa	Sargant, 1973 (83)
Windigo	A delusion of being possessed by a cannibalistic monster (Windigo)	Canadian Indians	Teicher, 1961 (84)

difference remains a significant challenge to the AS addiction hypothesis.

Although case reports have documented substance-dependence treatment seeking in AS users, the extent of this treatment-seeking behavior seems small. Clancy and Yates (66) 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 during a 1-year period. Those reporting AS-using patients did note DSM-IV-TR psychoactive substance dependence for AS. However, the limited treatment-seeking behavior in AS users also challenges the validity of the AS addiction hypothesis.

Biologic mechanisms for addiction with AS compounds have received limited research attention. There is no current animal model for addiction to AS. 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. A recent study supports an animal model for androgen reinforcement (67). This model suggests the reinforcing effect of androgens in animals is milder than for alcohol or cocaine.

Presently, the AS addiction hypothesis is unproven. Further epidemiologic, clinical, and basic science study will be necessary to more completely understand the psychopharmacology and psychiatric effects of these compounds.

4. Eponyms and Cultural Syndromes

Eponyms and cultural syndromes important in psychiatry are summarized in Tables 17.6 and 17.7 (68–84).

These categories have been the subject of review (85). Knowledge of these descriptive syndromes underscores the role of the history of psychiatric nosology. Knowledge of cultural syndromes underscores the effect of environmental and cultural influences on the phenomenology of psychiatric syndromes.

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Part II
Child Psychiatry

18
Disruptive Behavior Disorders

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Abstract Attention-deficit hyperactivity disorder (ADHD), oppositional defiant disorder (ODD), and conduct disorder are a heterogeneous group of childhood onset behavioral disorders that are traditionally lumped together as Disruptive Behavior Disorders (DBD) because they share behaviors that 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, and defiance; and conduct disorder by aggression, deceitfulness and violation of the 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 regarding the DBDs, 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, sex, 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 focuses on each condition separately.

Keywords Attention-deficit hyperactivity disorder · Children · Comorbidity · Conduct disorder · Disruptive behavior disorders · Gender · Preschool · Prevention · Psychopharmacology

1. Description, Symptoms

Attention-deficit hyperactivity disorder (ADHD) is a complex neurodevelopmental syndrome characterized by developmentally inappropriate dysregulation of attention, impulse control, and hyperactivity, that are 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 4.4 million children in the United States (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 approximately 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, social, and preschool and school 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, are associated with comorbid disorders and, depending on personality and psychosocial factors, lead to lifelong maladaptations and economic, social, and emotional adversity. The economic impact associated with decreased occupational performance alone is calculated to be approximately $77 billion/year through absenteeism, low productivity, and salary loss (4).

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Because of its high prevalence and because of the evidence that early diagnosis and treatment clearly diminish the virulence 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). In addition, because the vast majority of children with ADHD are treated by primary care physicians, rather than by 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, sex, 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). In addition to 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, 11). Healthcare costs for children with ADHD are approximately twice as high as for control subjects in community settings (11). 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, many individuals 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, and John F. Kennedy, 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 (12), 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, in which the understanding of ADHD as an executive function dysfunction is being broadened to include affective and neuromotor disturbance. 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 (13), on the other hand, 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; because it cannot be diagnosed by objective laboratory tests, nor does it show consistent neuropsychological deficits (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 children (or adults) themselves. 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.

2. DSM-IV ADHD Criteria

An explosion of information regarding psychosocial, biologic, and neuropsychological correlates of ADHD and other neuropsychiatric disorders has been gained in the last 20 years. However, ADHD 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 (*D*isorder of *A*ttention, *M*otor control and *P*erception; a system used primarily in Scandinavia) (15). However, The *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (DSM-IV) classification system (16) is the prevalent system in the United States, and increasingly is also applied 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 current DSM-IV criteria are based on reworking of previous ADHD criteria and on extensive field trials of ADHD symptoms, whereby two behavioral dimensions are identified, one associated with inattention and cognitive disorganization, and the other with impulsivity and hyperactivity, occurring alone or in combination, resulting in the three subtypes that represent the current operational definitions: ADHD predominantly inattentive (ADHD-I), predominantly hyperactive–impulsive (ADHD-H), and combined subtypes (ADHD-C). ADHD not otherwise specified (ADHD-NOS) may be diagnosed if full

symptom criteria are not met but impairment is established. Accumulating data of differences in cognitive, behavioral, and affective symptoms associated with the basic dimensions of attention and impulsivity–hyperactivity are leading to further "splitting" of the subtypes, but the DSM continues, for the time being, to provide the roadmap for clinical and diagnostic applications (Table 18.1).

Several areas of discussion are associated with DSM criteria, regarding the age of onset, the occurrence across contexts, and the exclusionary criteria (17):

Criterion B: Age of onset: ADHD usually manifests by age 4 years in children who are disruptive, impulsive and hyperactive, but diagnosis of the predominantly inattentive type may be delayed because inattention and cognitive disorganization may not be noticed in the preschool and early elementary years and may become impairing only when academic and organizational demands accelerate in the later school grades.

Criterion C: Cross-situational impairment 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: Criterion D refers to the requirement for clear evidence of functional impairment. The core impairments in ADHD are academic underachievement and poor peer relationships because of 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 (24). Gordon and colleagues (24), 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-IV 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 (24).

Criterion E: The exclusionary criteria cannot consistently be applied regarding autism spectrum disorders (ASD) and mood disorders, given the high degree of overlap of impulsivity, hyperactivity, and attentional dysregulation in high-functioning as well as low-functioning children with ASD (20), and the frequent comorbidity of mood disorders with

TABLE 18.1. DSM-IV criteria for ADHD.

A. Either (1) or (2)
   1. Inattention: at least six of the following symptoms of inattention that have persisted for at least 6 months to a degree that is maladaptive and inconsistent with developmental level:
      (a) Often fails to give close attention to details in schoolwork, work, or other activities
      (b) Often has difficulty sustaining attention in tasks or play activities
      (c) Often does not seem to listen to what is being said to him or her
      (d) Often does not follow through on instructions and fails to finish schoolwork, chores, or duties in the workplace (not caused by oppositional behavior or failure to understand instructions)
      (e) Often makes careless mistakes in schoolwork or work
      (f) Often stares into space (and reports daydreaming when questioned)
      (g) Often has difficulties organizing goal-directed activities
      (h) Often seems to be apathetic or unmotivated to engage in effortful goal-directed activities that are not of intrinsic interest
      (i) Often loses things necessary for tasks or activities (e.g., school assignments, pencils, books, tools, or toys)
      (j) Often forgetful in daily activities
   2. Hyperactivity–impulsivity: at least five symptoms of hyperactivity–impulsivity that have persisted for at least 6 months to a degree that is maladaptive and inconsistent with the developmental level:
      (a) Often fidgets with hands or feet or squirms in seat
      (b) Often leaves seat in classroom or in other situations in which remaining seated is expected
      (c) Often runs about or climbs excessively in situations in which it is inappropriate (in adolescents or adults, may be limited to subjective feelings or restlessness)
      (d) Often talks excessively
      (e) Often acts as if he or she is driven by a motor and cannot remain still
      (f) Often has difficulty playing or engaging in leisure activities quietly
      (g) Often interrupts or intrudes on others (e.g., butts into others conversations or games)
      (h) Often blurts out answers to questions before the questions have been completed
      (i) Often has difficulty waiting in lines, or awaiting turn in games or group situations
B. Onset no later than 7 years of age
C. Symptoms must be present in two or more situations (e.g., at school and at home)
D. The disturbance causes marked distress or significant impairment in social, academic, or occupational functioning
E. Does not occur excessively during the course of a Pervasive Developmental Disorder, Schizophrenia, or other psychotic disorder, and is not better accounted for by a Mood Disorder

ADHD (9). This overlap will be discussed further in Sect. 4, regarding comorbidities.

The DSM-IV symptom checklists are prefaced with the requirement that the behaviors are maladaptive and inconsistent with the developmental level. 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 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 (21). 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 (22). The parental expectations, socioemotional health, and possible observation bias of the caretakers must, therefore, be considered, and observations of individuals who are less involved 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 (23).

2.1. Subtype Characteristics

Considerable clinical and neuropsychological differences between subtypes indicate the heterogeneity underlying the diagnosis. Differences are found with respect to sex distribution, functional impairments, comorbidities, and pharmacologic response (25, 26). Hyperactivity is the symptom driving behavioral impairment and its comorbidity with oppositional defiant disorder (ODD), whereas attention problems drive academic impairment (27, 28). The combined type has the worst of both worlds, shows both academic impairment and ODD symptoms in approximately 50% of patients, and is the most common subtype in both sexes (28). The hyperactive–impulsive subtype is usually not associated with academic problems, and, in fact, is correlated with above average academic performance in a significant proportion of patients (27). However, approximately 30% of children are behaviorally at risk because of associated ODD symptoms (27).

The predominantly inattentive type of ADHD (ADHD-I) seems to be an altogether different disorder both clinically and etiologically. It is characterized largely by symptoms of cognitive dysfunction, underarousal, poor working memory, slow cognitive tempo, forgetfulness, and avoidance of mental effort (29). Children with ADHD-I are usually older at diagnosis, more likely to be girls, 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 the impulsive intrusiveness of ADHD combined subtype (ADHD-C). ADHD-I has low comorbidity with ODD symptoms, has a higher proportion of girls than the other two subtypes in community samples (1:2), and is found twice as frequently in girls than boys in referred samples (2:1) (30). Because children with the inattentive type are not disruptive, problems may go unnoticed, they are underreferred, and often only identified when comorbidities or academic problems emerge.

3. Epidemiology

3.1. Prevalence

ADHD is the most frequent chronic behavior disorder in preadolescent children. Prevalence rates vary from 3 to 12% in large epidemiologic studies, with 6.7 to 7.5% appearing to be the most consistent range. The National Survey of Children's Health conducted by the CDC from 2003 to 2004 and based on telephone interviews with more than 100,000 families reported that 7.8% (4.4 million) US children aged 4 to 17 years had ever had a diagnosis of ADHD. The rate in boys was reported to be 11%, approximately 2.5 times the rate of 4.4% in girls. The rates increased with age: 4% in children younger than 9 years; 9.7% in children 9 to 17 years old. At 16 years of age, boys had a reported rate of 14.9%; and at 11 years, girls showed their highest rate of 6.1%. There were large prevalence differences by state: Colorado, 5%; Alabama, 11.1%. There were no significant racial differences (white, black, multiracial), but Hispanics reported significantly lower rates of diagnosis than non-Hispanics. ADHD was reportedly diagnosed more frequently in boys living below the poverty threshold, whereas girls did not show such differences (2).

A review of international prevalence rates (31) found that ADHD can be identified as a clinical diagnostic entity in all countries studied, but that rates vary according to diagnostic methods, criteria, and population samples; ranging from higher to significantly lower rates. When strict DSM criteria are applied to comparable cohorts, rates are not dissimilar to those in the United States. The fact that ADHD is increased 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 the diagnosis of ADHD with socioeconomic and demographic factors, i.e., family characteristics such as less likely to live with father, more likely to be poor; and 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 (24).

3.2. Sex

Until recently, 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 in girls, therefore, 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 3:1 male to 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 sex, 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 sexes seem 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 sexes 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 approximately 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 control subjects. 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 sexes, with a higher risk for substance abuse disorders and antisocial personality disorders in men (38).

3.3. Age

3.3.1. Infants

Most studies of ADHD are limited to children in middle childhood (6–12 years). However, data is becoming available regarding the developmental precursors of psychopathology from infancy and toddlerhood, although the DSM classification system is poorly suited for these age groups. 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 (39).

Auerbach (40) 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) (41). Newborns at risk for ADHD showed risk factors 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 that disorganized, insecure attachment, emotional dysregulation, and sleep problems in infancy correlated with hyperactivity, ADHD, and conduct disorders at early school age (22, 42, 43). The infant behaviors may be mediated by negative parenting and/or parental psychopathology, specifically, maternal depression. Hostile parenting by mothers of sons seems to be a risk factor for later ODD and conduct disorder, whereas maternal depression is more strongly associated with ADHD (44, 45). A construct of parent–child interaction that may be a mediating factor for these effects is the presence and quality of parental, 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 seem to protect against the co-development of ODD/conduct disorder (44). Maternal responsiveness is also strongly associated with language development in early childhood, which, in turn, affects behavior regulation (46). 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 temperament factors (47).

Eric Erickson said: "The infant age of development is based on establishment of basic trust derived from earliest experience and is dependant on the quality of the maternal relationship" (48). And to follow with a quote from 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" (49).

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 approximately 50% of children considered to be at risk for ADHD, symptoms do not persist, and only 5 to 10% of preschoolers with concerns about inattention actually continue on to develop ADHD (50). ADHD subtype assignment is unstable in preschoolers as well as in school-aged children, therefore, children may meet criteria for different subtypes over time (51). Prevalence rates for ADHD in preschoolers are, therefore, very inconsistent, depending on methods and clinic versus community populations. The range is from approximately 2% in primary care pediatrics to 5.7% in the community to 59% in psychiatric referral clinics (50). In the Canadian nationwide survey of children 0 to 7 years old, children's behavior was rated by their mothers at 2 years old and again at 7 years old, with 7% of children showing persistence of hyperactivity at 7 years. The persistence was associated with male sex, maternal prenatal smoking, maternal depression, and hostile parenting (52).

At this age, persistent behavioral ADHD symptoms may indicate a host of disparate problems, from medical problems, such as gastroesophageal reflux, to environmental disruption and parenting effects, to the emotional and cognitive response to developmental frustration, to autism spectrum disorders (ASD). 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 result in equally dramatic emotional and behavioral stabilization. In contrast, impulsive, hyperactive, inattentive, distractible behavior is common in preschoolers with ASD, 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 diagnosis. Furthermore, cognitive deficits may underlie and mimic ADHD symptoms (21). 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 challenge—results in avoidance behavior, distractibility, and inattentiveness, verbal and nonverbal cognitive deficits should be excluded.

Preschoolers with ADHD show deficits and differences from control children in intellectual, sensory, and motor performance that go beyond the core symptoms of ADHD (21, 53). Although similar deficits have been found in school-aged children with ADHD, there is a paucity of data regarding 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.

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 because 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, 54).

There are many ways in which ADHD children differ from their unaffected peers. Causal connections, story comprehension, and time perception are deficient compared with control subjects (55, 56). Children with ADHD show restricted cognitive flexibility (57), 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). Children with ADHD have a difficulty starting and completing tasks and have difficulty self-monitoring (58). They are often clumsy with complex fine motor tasks (59) and in visual–motor integration, which manifests in poor handwriting and impairment in written schoolwork. Adaptive function in daily living skills, such as maintaining hygiene, or taking on household responsibilities, are immature relative to cognitive levels (60). Although they are inattentive and distractible with chores, homework, and even on the sports field, they may spend hours transfixed watching television or playing computer and video games. They are emotionally and behaviorally very context dependant (55), for instance, they 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 (61).

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 caused by core ADHD symptoms and associated cognitive, language, and learning disabilities, which are found in 30 to 50% of patients (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 (62), which seems 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 (62). Academic performance, in fact, may not be an issue in a bright child with ADHD, but their 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 behavior, substance abuse disorders, and school and occupational failure in adolescence and adulthood (63).

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" (48).

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 seems 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 (23, 64). Impairing symptoms continue into adolescence in 60 to 85% of children with ADHD, with only a small minority showing remission. Hyperactivity decreases, but inattentiveness and impulsivity persist (54). Comorbidities with anxiety disorders, depression, and dysthymia increase from the already high rate of approximately 30% in middle childhood to 35 and 50%, respectively, by mid-adolescence. Adolescent-onset mania may be suspected in depressed children who have chronic irritability and explosiveness (9). Quality of life is affected in all domains: 50 to 70% of children with ADHD have few or no friends, the school drop-out rate is estimated at 32 to 40%, and the college completion rate is 5 to 10% (10, 65, 66). Adolescents with ADHD are at a twofold to fourfold higher risk than normative peers to be involved in automobile accidents (67); other risk-taking behaviors are increased, such as unprotected sex, with an increased teen pregnancy and sexually transmitted disease (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 (62). ADHD has also been correlated with bulimia in obese adolescents of both sexes, independently of mood disorders (68).

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 hand by adolescent-specific cognitive and affective development, increased introspection, and self-appraisal (69). 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 drop-out 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.

3.3.5. Adults

Although this discussion regarding ADHD is restricted to children, mention of adult ADHD is appropriate, because 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 seems that impairing ADHD symptomatology persists into adulthood in approximately 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 (70). The adult prevalence is estimated to be between 4 and 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 control subjects (1, 10, 70, 71). 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 men may be as high as 40%, and is highly associated with learning disabilities and affective disorders (72).

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 function of the individual is affected (73). Awareness of this high likelihood of comorbidity, and diagnosis and interventions has the same urgency as treatment of ADHD to decrease the severe psychosocial stressors that are the inevitable consequences for the child and their family (74). 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.

4.1. ADHD and Developmental Disorders

Children with ADHD are different cognitively as well as affectively from children without ADHD. Approximately 30 to 50% of children with ADHD have other neurodevelopmental disorders, such as dyslexia and language disorders. It seems 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 seems, instead, that they may be etiologically multifactorial, in that disparate conditions share genetic and cognitive traits that account for their co-occurrence (75). The surprisingly high rate of 25 to 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 to 50% of children with ADHD (76), 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 (77). Language disorders that persist into adolescence are, in and of themselves, associated with a higher degrees of cognitive, behavioral, and emotional disturbance (78); 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 (79).

Children with Asperger's syndrome and ASD have a 20 to 50% rate of comorbid ADHD as well as the characteristic social–communication deficits (80). Developmental coordination disorder is identified in approximately 50% of children with ADHD, and indicates more severe cognitive involvement as well as psychopathology (81). Approximately 60% of children with Tourette's syndrome have comorbid ADHD, which may be a distinct behavioral and possibly neurobiological manifestation of ADHD (82).

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 (80).

4.2. Psychiatric Comorbidity

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 with 2 to 5% of control subjects. The association of Bipolar Disorder to ADHD is, as yet, somewhat unclear, but it is thought that early hyperactivity may actually represent or develop into mania in 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. Anxiety disorders were found in 28% of children at the baseline age of 11 years, and increased to 35% in middle adolescence, compared with 5% and 9%, respectively, in healthy children. Characteristically, anxiety (overanxious disorder, separation anxiety) and depression are found concurrently in ADHD. The severity and degree of impairment is mediated by number of comorbid conditions, family–genetic factors, and age of onset (83), i.e., the earlier the onset, the more severe the manifestations.

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, early infant, and childhood biological and experiential factors (83, 84). In this context, it is very 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 (85). The importance of prenatal and early childhood environmental/psychosocial contributions to childhood mental health and developmental disorders cannot be stressed enough, because prevention and early intervention are realistic goals for many of the identified risk factors (86).

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 hypothalamic–pituitary–adrenal (HPA) axis, 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 (83) 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 (87), 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 (45). The cumulative effects of poor peer relationships and academic impairments represent the specific risk factors for the development of depression in ADHD (62, 83).

4.2.3. Oppositional Defiant Disorder

ODD can be identified in approximately 40 to 60% of children with ADHD, predominantly combined type, in approximately 30% of children with the predominantly hyperactive type, and is rarely reported in 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, and 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 very 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 (22, 45). 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 (88–90), and paternal negativity are contributing factors (83), 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 (90). ODD is associated with intense family conflict (91), that is especially virulent in adolescence and potentiates the negative effects of core ADHD behaviors (92, 93). 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 (88). Conduct disorder is clearly separable from both ADHD and ODD, and will be discussed separately.

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. Second, 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 syndrome and effects; 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 (94).

Any chronic illness, anemia, asthma, allergies, heart conditions, renal disease, metabolic dysregulation (such as in diabetes or thyroid disease), chronic gastrointestinal (GI) 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 (95).

Furthermore, many medications have side effects that may affect attention and cognitive processing in some children, most significantly neuroleptics, anticonvulsants, steroids, antihypertensives, bronchodilators, and antihistamines.

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 19th and early part of the 20th century (12, 96). 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 during the last decade focusing on the delineation of executive functioning and inhibitory deficits in the disorder (8, 97, 98). 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 (97, 99). 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 (100–102). 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 (PFC) (especially the inferior frontal gyrus), anterior cingulate, caudate, and thalamus (103–105). However, whether response inhibition deficits—or even executive functioning or PFC deficits more broadly—constitute the core or primary deficit in ADHD remains under considerable debate (106, 107). For instance, attention and arousal factors (e.g., variable performance and slower responding) likely also contribute to response inhibition deficits (108). In addition, recent 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 10% of children had generalized/global impairments across executive functioning measures (i.e., on five or more executive functioning measures) (109). 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-IV).

The considerable neuropsychological heterogeneity among children diagnosed with ADHD has moved the field toward 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 (109, 110). This approach aims to identify possible pathways to disorder—including potentially numerous genetic and environmental influences—and attempts to improve on the DSM-IV's behaviorally based taxonomy by increasing specificity of the ADHD construct. This recent 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 (111–113). For instance, Sergeant and colleagues' cognitive–energetic state regulation theory of ADHD (114) 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" (114). Other prominent theories of ADHD argue the disorder to result from temporal processing deficits (115, 116), abnormalities in reinforcement–response mechanism (e.g., reward circuitry) (117), or interactions between altered reinforcement–response mechanisms and environmental factors such as social learning, environmental conditioning, and altered appetitive or motivational systems (118) that produce "delay aversion" (119, 120).

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 (121). This research may, however, be confounded by the DSM-IV 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, because some evidence suggests that children with "sluggish cognitive tempo" (e.g., inconsistent alertness and underactivity) may represent an etiologically distinct neuropsychological subtype of ADHD (122). The neuropsychological pathways toward comorbidity in ADHD are also relatively underspecified to date. Temperamental vulnerabilities (e.g., negative emotionality), for instance, may predict development of comorbid oppositional or antisocial behavior disorders in ADHD independently of cognitive deficits (112, 113). Likewise, ADHD-related neurocognitive impairments may predispose children toward the development of comorbid learning disabilities (123, 124). 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 (111, 125) that persist into adulthood, despite the waning of behavioral symptoms such as hyperactivity and impulsivity (126–128).

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. 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. Neuropsychological and neuroimaging studies, however, are inconsistent and variable in demonstrating the localizations as well as functional deficits, and actually contradict a unitary cause for or discrete pathways of neural dysfunction. Indeed, the variability is hypothesized to be the result of differential disruptions that may occur during the development of the brain in fronto–striatal–cerebellar–parietal circuits, which are the putative neural substrates for inhibitory and attentional control, 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 that are likely to affect others in secondary ways, especially in a dynamically changing system such as the developing child with ADHD" (129).

6.1. Neuroimaging

Anatomic evidence for involvement of the frontal–striatal–cerebellar circuits is based on volumetric studies that demonstrate differences of the cerebellar vermis, caudate, putamen, and globus pallidus morphology in ADHD subjects compared with control subjects, as well as frontal lobe differences, with smaller volumes described of medial frontal areas including the cingulate, prefrontal, premotor, and motor cortex (130). In contrast to finding volumetric changes in discrete regions, Castellanos (131) found the 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 healthy subjects as well as hyperactivity–impulsivity in ADHD children. Significantly, morphologic changes were the same for children taking stimulants as for untreated children. Functional magnetic resonance imaging (fMRI) studies demonstrate activation differences in attention processing tasks in striatal–frontal networks (132), and in inhibitory control tasks of cingulate, ventrolateral, and dorsolateral PFC between ADHD and control subjects, but, comparable to the Castellanos findings, no differences were identified between treated and stimulant-naive ADHD subjects (105, 133). Acute methylphenidate (MPH) challenge enhances brain activity on fMRI scanning, but this response to MPH is inconsistent, not reflected in clinical test performance, and does not correspond to the fMRI activation patterns between ADHD probands and control subjects (132).

Affective response and mood disturbances in ADHD are thought to be correlated with volumetric differences in amygdala regions found in children with combined ADHD and are interpreted to represent alterations in interconnectivity between amygdala nuclei and the PFC. Differences in hippocampal volume are speculated to account for differences in delay aversion and stimulus-seeking behavior (134). Further evidence for frontal involvement are electroencephalogram (EEG) studies demonstrating cortical slowing (135, 136), and enhancement of theta activity in frontal quadrants in ADHD, with male subjects having more generalized and female subjects having localized frontal changes (137).

It is unclear how specific neuroimaging findings are to ADHD and how much they overlap with other forms of neuropathology. It seems likely that structural–functional relationships are bidirectional, and affected by developmental and environmental factors (130). 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.

6.2. Neuromodulators

ADHD symptoms seem to be mediated by alterations of the availability and effect of the catecholamines dopamine and norepinephrine, which activate the circuitry and projections between the PFC, basal ganglia, and cerebellum. Moderate levels of these catecholamines enhance, and high levels inhibit PFC function. Localization and effect of dopamine is dependant 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., their stimulation enhances working memory and attention regulation at lower levels of dopamine, but impairs working memory and attention regulation at high levels, such as with stress. Much less is known regarding dopamine-2-type receptor dysfunction, which seems to be associated with schizophrenia, and, although 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 they seem to inhibit GABAergic (inhibitory) activity in PFC pyramidal cells; stimulation of D4 receptors consequently increases pyramidal cell firing. It seems that D4-receptor dysfunction, which results in increased GABA activity in the PFC with decreased pyramidal cell firing, may be associated with ADHD (138–140).

Norepinephrine receptor activity may enhance or impair the 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 (138).

7. Etiology

The many changes the concept of ADHD has undergone over time reflect different ideas regarding 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, 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 (22, 86). This research gives support to the feasibility of prevention or at least mitigation of physical as well as mental disorders (86).

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% (141, 142). 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 (141–143). 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 (142, 144). 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 the 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 DAT and dopamine receptor (DRD) mechanisms. Multiple candidate genes have been studied, with inconsistent evidence that *DAT1* and dopamine receptor *DRD4*, and *DRD5* polymorphisms confer susceptibility to ADHD (142, 143). A meta-analysis of 113 genetic studies by Bobb, Castellanos, and colleagues (145) support a definite but modest role for dopamine D4 and D5 receptors, and dopamine and serotonin transporter genes in ADHD. An association of the *DRD4* seven-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 (146).

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 (147). This approach is related to the concept of "endophenotype," which has recently 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 (148). 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 (110).

An example of the genotype–phenotype linkage approach is the study by Barkley and colleagues of the clinical phenotypes associated with identified susceptibility genes in children with ADHD and control subjects enrolled in the Rochester Longitudinal Study (149). 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 (149). 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.

Epigenetic factors as mediators between molecular genetic and environmental agents are as yet unexplored in the etiology of ADHD.

7.2. Physical Environmental Factors

Many studies demonstrate the effect of early environmental adversity and influences on developmental outcome (22, 86). 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 (150).

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 to 3.5 when corrected for other biological and psychosocial variables (151). Most epidemiologic studies have focused on combined-type ADHD and externalizing disorders and found a strong association with prenatal smoking and nicotine exposure (152), but a recent careful case–control study of 100 middle-class children with inattentive-type ADHD found an odds ratio of 3.44 for ADHD if mothers smoked more than 10 cigarettes/day compared with 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 (153).

Smoking has developmental and morphologic effects through multiple pathways, including increased CO, decreased oxygenation, cadmium accumulation, and 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 (154). 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 (155). Increased prenatal cortisol exposure is associated with long-lasting behavioral effects, which include not only ADHD but anxiety and depression (156). 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 with exposed children with either or no polymorphism (157).

7.2.2. Prenatal Alcohol Exposure

The teratogenetic effects on multiple organ systems of prenatal alcohol exposure, which is estimated to occur in 16% of pregnancies in the United States, are well known (158). It is estimated that 1% of live births show alcohol-related neurodevelopmental disorder (ARND). Alcohol affects neuronal migration, myelination, and neurogenesis. 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 (159–161).

Alcoholism is found in up to 25% of parents of children with ADHD (162). ADHD has been reported in 41% of children referred for evaluation of prenatal alcohol exposure, and it usually occurs within a spectrum of significant cognitive and behavioral deficits (163). Stimulants are less effective in treating ADHD in alcohol-exposed children (164), and alternatives must frequently be sought.

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 sex of the child, account for a much higher proportion of the behavioral variance than alcohol itself (158). However, even minimal amounts of prenatal alcohol exposure within an adverse social environment potentiate the behavioral risk when compared with control subjects. 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 (158). 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 (162).

7.2.3. Environmental Pollutants

The neurotoxic effects of lead and mercury are well researched and they 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 (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 (86, 165).

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 as well as physical morbidity, both protein–energy malnutrition (PEM) and micronutrient deficiencies during the course of early brain development are etiologically associated with deficits in cognitive function and ADHD (166–168). PEM affects 22 to 35% of poor US children and at least one third of children in the developing world (169). 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 PEM only in the first year of life, but not later, compared with a 15% incidence in control subjects (170). 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 United States: 13% of 1-year-olds, 5% of 2-year-olds, and 9 to 11% of adolescent and young adult women are shown to have iron deficiency, of which only 2 to 5% had iron deficiency anemia (171). Multiple studies show attentional, memory, and learning impairment in anemic and non-anemic 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-aged and older children has also been shown to normalize the cognitive–behavioral effects (172).

Long-chain polyunsaturated essential fatty acids (EFAs), specifically omega-3 fatty acids have been studied not only in terms of cardiac and immunologic effects but for their role in brain development and function. Omega-3 fatty acids are structural elements of cell membranes, neurotransmitters, and are substrates of signaling molecules, modulators in the regulation of gene expression, and they have played a central role in the evolution of the brain (173). Omega-3 fatty acids 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 (174). 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 (174). 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 (175).

7.2.5. Other Dietary Factors

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. Studies of obese children also have found no direct relationship between ADHD and obesity.

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 (176), 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. Initial diet trials did not provide evidence to support Feingold's theory but did

imply that some children may have preexisting neurochemical disturbances that make them particularly sensitive to food dyes. Food allergens as well as additives and multiple, rather than single offending agents, have been hypothesized as contributing to behavioral symptoms (177). Double-blind placebo-controlled studies of benzoate preservatives and food dyes showed behavior effects of both in 3-year-old children (178). Several individualized elimination and challenge studies have demonstrated that specified foods and food dyes change behavior in a significant number of children with ADHD, whereby family histories of food allergies and migraines provide a genetic basis for the response (177,179). Sugar and aspartamate, which had been frequently implicated, were shown not to produce or affect ADHD symptoms (180).

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.

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 (181). 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 EFA 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 recent meta-analysis of premature outcomes (182), 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 (182). 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 with casual) attention with cognitive as well as hyperactivity measures at 5 years of age, with risk mediated by male sex, gestational age, and maternal education (183). Other longitudinal studies have shown strong relationships between VLBW, cognitive deficits, emotional dysregulation, and lower socioeconomic status (SES) at 2 years (184); and internalizing problems, peer rejection, and inattention in late adolescence (185).

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 sex, age, and SES/maternal education. Early anticipatory guidance should start in infancy to mitigate psychiatric and behavioral morbidity.

7.4. Chronic Hypoxia

Chronic, even mild degrees of oxygen desaturation may cause cognitive and attentional dysfunction. Cyanotic CHD and sleep disordered breathing are both relatively common. The evidence is robust that the hypoxia associated with both is causative for ADHD (95). 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 (95).

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 that may last into adulthood. After birth, the responsiveness of the primary caretakers to the infant seems 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 (186) 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. Child factors that may inhibit maternal reciprocity are also significant, such as poor maternal–child temperamental "fit," child illness with increased internal distractibility caused by 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 (187). 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 (188).

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). Fifty percent 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 (189). This study demonstrates the high correlation with and cumulative effect of maternal and child problems. Unfortunately, there is no information regarding the factors that were associated with positive child outcomes (~75%) in this study.

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 (190,191). However, causality and directionality (i.e., does TV cause ADHD or does ADHD predispose to more TV viewing?) cannot be ascertained in the absence of longitudinal and controlled studies. 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 (192). In older children, an association between time spent playing video games, school performance, and symptoms of inattentive-type ADHD has been found (193).

8. Evaluation

Because the majority of children with ADHD are treated by their primary care physicians, the AAP has issued guidelines for evaluation and management of ADHD that are virtually congruent with the preliminary guidelines by the AACAP (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. Assessments need to be based on DSM criteria and need to include information from parents or caregivers and classroom teachers 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. Because ADHD increases and becomes more virulent with psychosocial adversity and comorbidities, information regarding preceding and ongoing social/familial stressors and family and emotional functioning should be obtained.

8.1. The Diagnostic Interview

The diagnostic interview with the parents as well as the interview with the child, and, if possible, observation in a challenging situation, are central to the evaluation. The interview with the parents should be held separately from the child's interview 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, exclusion of 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 exclude significant social, thought, or emotional problems.

The physical and neurological examination should be made with respect to excluding associated or underlying medical conditions, which are, in effect, infrequent. However, in approximately 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.

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 (194). Several of these scales are free and in the public domain and can be downloaded (194). 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 coalmine" and quickly display problems with environmental "fit." Children with learning disabilities 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.

8.3. Developmental/Psychological Assessments

Because 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 status, 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 exclude 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 exclude 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, and 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.

9. Treatment

ADHD is a chronic disorder, therefore, quality of life considerations of the child within their family, school, and peer context should be at the center of treatment planning. Similar 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. Very 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 reevaluated. 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.

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 (195), although short-term treatment does not seem to offer any benefit beyond that obtained by optimal medication management (196). 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 may be associated with unacceptable side effects (197). 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 (198,199).

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 regarding state and community resources. Early Head Start, a good daycare, or preschool may provide an emotionally neutral environment that may relieve stress for the child as well as the family and improve family interactions.

Schoolchildren 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 learning disabilities 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 learning disability 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 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 used, i.e., it has no curative potential, but it does, however, teach self-control, social skills, and coping strategies (200).

9.2. Pharmacologic Treatment

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 (201). Amphetamines were not routinely used in ADHD until the less potent stimulant methylphenidate (MPH; Ritalin) became available in the 1960s. Since then, MPH has become the most frequently used and studied psychotropic agent in children, and stimulants have become the "gold standard" for treatment effectiveness in ADHD (202). 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 healthy subjects as well as ADHD subjects with low doses of MPH is the basis for improvement of clinical symptoms. Stimulants affect norepinephrine and dopamine release predominantly in the PFC 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 (139).

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 conduct disorder symptoms even in the absence of ADHD symptoms (139). Stimulants are effective in all ages, starting with preschoolers (203). 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 to 75% of children with ADHD, with relatively few side effects. However, the application of the outcomes of clinical research trials versus the outcome in community settings is problematic, because clinical research trials have a strong sample bias compared with 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 versus *effectiveness* of a treatment, i.e., the treatment response under usual clinical conditions, should, therefore, be kept in mind. Global Assessment of Functioning scores and quality of life measures as outcome measures are being introduced to bridge this deficit (204).

Compared with the abundance of short-term randomized trials of stimulants, mostly of MPH, 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) (205), a multicenter randomized prospective study that compared community (including

pharmacological) treatment, intensive pharmacological treatments (mostly MPH), and behavioral treatments alone and in combination with pharmacological treatment, during the course of 14 months in 579 children. The study found that, compared with behavioral and community treatments, pharmacological treatment alone was superior to all other conditions in treating core ADHD symptoms. However, combination treatment was somewhat 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 (205).

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. Approximately 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-aged boys, but similar effectiveness in girls, adolescents, and adults has been demonstrated (5,205). 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 recent Preschool ADHD Treatments Study (PATS), a combination of blinded randomized and open-label study of 1 year's duration in children aged 3 to 5 years, demonstrated that stimulants are also efficacious in preschoolers, who tended to require and tolerate lower doses but had an increased incidence of side effects (203).

9.2.1.1. Stimulant Forms

MPH, 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 approximately twice as potent as MPH. Pemoline, a long-acting stimulant with an extended half-life, is used much less frequently because of its association with severe liver toxicity and the necessity for frequent monitoring of liver function. The effect size of stimulants, i.e., the difference between drug and placebo effects, is 0.8 to 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 (206).

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 levels and possible withdrawal/rebound symptoms at trough levels, and allows for adjustment of medication to daily routines, meals, and bedtimes.

Short-acting MPH/MAS/D-amphetamine onset is after approximately 30 minutes, and the duration of effect is approximately 3 to 5 hours. For intermediate-acting preparations (Metadate CD, Ritalin LA), onset is after approximately 1 hour and the duration is approximately 8 hours. Sustained-release preparations (OROS-Methylphenidate/Adderall XR MAS) have an onset of approximately 1 hour, with a duration effect of 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 in an osmotic release form, affect absorption and availability. Once daily, 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 (207–209).

A MPH dermal patch (multipolymeric adhesive system; Daytrana), releasing 10 to 30 mg of MPH during a 9-hour period, has recently been approved for children 6 to 12 years old and may be practical in children who are not able to take oral medications. It has been found to be safe and effective in short-term studies (210). There are anecdotal reports of local and systemic sensitization, however, which is a risk with all topical medications. The 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 (195).

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.

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 ASD; 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 (211). In ADHD with comorbid tic disorders, stimulants are not a contraindication when carefully monitored (212), but should be discontinued if tics worsen or do not stabilize with alpha-adrenergic agonists (clonidine, guanfacine) (213), 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 (214). Alternatively, selective serotonin reuptake inhibitors (SSRIs), venlafaxine, or tricyclic antidepressants (TCAs) may be necessary, the latter having significant alpha-adrenergic effects but requiring 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 coocurrence after mood stabilization (215).

9.2.1.3. Stimulant Side Effects

Stimulants have a high margin of safety. Most side effects are a result of the central nervous system action of stimulants and, therefore, are behavioral or emotional. However, stomachache and headache are frequent, and are usually mild and of short duration. Absorption is affected by calcium and citric acid, but not by other foods, so that stomachaches can be ameliorated when stimulants are taken with a meal. Appetite suppression is frequent and chronic, but can be compensated for with a good breakfast, dinner, and bedtime snack. Children should have a snack when levels are declining after short-acting or intermediate-acting dosages 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 (216). Social withdrawal, emotional and activity constriction, and obsessive–compulsive behavior may be signs of overmedication and should lead to dosage adjustment. In some children, increasing hyperactivity may be a sign of over rather than under medication. “Roller coaster” and withdrawal effects are seen more often with 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 (213). Contrary to public opinion, stimulants do not promote substance abuse and, in fact, show a protective effect to non-alcohol substance use when compared with persons with ADHD who have not been treated (217).

Occasionally, stimulants cause increased diuresis and enuresis because of a minor diuretic effect. Bone-marrow suppression and leukopenia occur very rarely. There are no established recommendations regarding monitoring of complete blood cell count (CBC).

Cardiac Effects. Stimulants do have cardiovascular effects, and may decrease heart rate and increase diastolic and systolic blood pressure at standard therapeutic doses (218). The recent furor over sudden cardiac death reported in 12 children during stimulant treatment with Adderall, however, is not supported by clinical data (219): sudden death on Adderall is calculated as 0.5:100,000 patient-years as compared with 1.3 to 8.5:100,000 patient-years in the general pediatric population. Sudden death in children is most often caused by fatal arrhythmias caused by CHD, such as long QT syndrome and hypertrophic cardiomyopathy. Five of the 12 reported cases had unrecognized underlying structural heart disease. Screening for a family history of sudden cardiac death, physical examination, and electrocardiogram (ECG) before beginning stimulant therapy is advised in children and adults. The combination of the cardiotropic alpha-adrenergic drugs and stimulants should be carefully monitored for hypotension and arrhythmias or bradycardia.

TCAs and monoamine oxide (MAO) inhibitors should not be given with MPH because MAO inhibitors increase TCA levels, increasing the risk of cardiotoxicity or hypertension. Stimulants are contraindicated in patients with significant arrhythmias, hypertension, liver disease, severe anxiety, and drug-seeking behavior (219).

Stimulants and Growth. The effect of stimulants on growth has been a topic of controversy for some time, and has been reactivated because of findings on the PATS, which monitored children during 12 months of stimulant treatment. In this group of children, linear growth decelerated by 20% of expected growth in 1 year, with a moderate effect on weight (220). 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-aged children (221). No information is currently available regarding the long-term growth trajectories of children started on stimulants as preschoolers. Appetite suppression and weight loss are frequent effects that have been thought to cause decreased linear growth when stimulants are given for long periods of

time. Data at this time is inconclusive but indicates that stimulant use in preschoolers needs precise justification. Although, recently, continuous year-round dosage regimens are advocated, careful consideration should be given to providing drug holidays and customizing the medication and dosage regimen to target times as well as symptoms in preschoolers.

9.2.2. Nonstimulant Medications

Fifty to 70% of children respond to stimulants, but alternate medications and nonpharmacological and supportive interventions are necessary for the other 30 to 50% who do not respond.

9.2.2.1. Atomoxetine

Atomoxetine (Strattera) (206) has displaced the alpha-adrenergic drugs, clonidine and guanfacine, for second-order medications for ADHD. Atomoxetine is a norepinephrine reuptake inhibitor, has no abuse potential or motor or tic activation, and does not interfere with sleep. Its effect size is significantly less than that of stimulants, at 0.6 to 0.72. Full effect is reached after 4 to 6 weeks of therapy. The dose is 0.5 mg/kg/day in one or two divided doses, and 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-naïve children rather than in those previously on stimulants. Atomoxetine 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, co-medication 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 of 1,357 children on atomoxetine, leading to a US Food and Drug Administration (FDA) black box warning (222).

9.2.2.2. Modafinil

Modafinil (Provigil) (206), originally indicated for narcolepsy, was recently approved by the FDA for treatment of ADHD in children. 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 to 9 days, to an average dose of 300 to 400 mg/day. Side effects are headache, appetite suppression, nervousness, and sleep disturbance.

9.2.2.3. Alpha-2 Adrenergic Agonists

The antihypertensive drugs clonidine and guanfacine (206) inhibit catecholamine release, affect basal adrenergic tone, and improve PFC function. They may be used alone or in conjunction with stimulants and are effective in impulsivity, hyperactivity, and aggression, especially in young children, and in treating ADHD-associated sleep disorders (223). Guanfacine is effective in tic disorders with ADHD, alone or in combination with stimulants (213). Clonidine and guanfacine have long half–lives, and behavioral effectiveness may not be observable for 4 to 6 weeks. The side effects of sedation and irritability may be significant initially, more so with clonidine than guanfacine. The potential for hypotension and bradycardia require ECG and blood pressure monitoring.

9.2.2.4. Antidepressants

The TCAs desipramine and nortriptyline have excellent effectiveness in improving the core symptoms of ADHD, and ADHD with comorbid tic disorders because of their noradrenergic effects (140). However, they have a narrow margin of safety because of their significant accumulation in cardiac and brain tissues, with a significant risk of cardiotoxicity resulting in conduction abnormalities, increased heart rate, and increased blood pressure. Effects are observed after approximately 4 weeks, dosages must be carefully titrated, and blood levels and cardiac response monitored with frequent ECGs. TCAs have significant anticholinergic side effects, and often cause weight gain and GI problems. Their use for ADHD has decreased sharply after reports of sudden cardiac death in several children (224).

Venlafaxine has both noradrenergic and serotonergic effects. It has shown moderate effectiveness in improving ADHD symptoms in adults with comorbid depression. However, short-term studies in children with ADHD showed significant side effects, no improvement of cognitive symptoms, and only moderate behavioral improvements; therefore, the risks outweigh the benefits in children (206). Bupropion is an antidepressant that does have noradrenergic and dopaminergic neurotransmission effects. Improvement of core ADHD symptoms in adults with comorbid bipolar depression is reported, but controlled studies in children are lacking (206).

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. Because many pathways lead to genesis of ADHD, a heterogeneity of effective interventions is

conceivable. A critical but open mind should be maintained toward novel approaches.

9.3.1. Biofeedback Modalities

Neurofeedback is a method of self-regulation that has been widely used clinically 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 cortex and PFC in the majority of patients with ADHD (135,136). Suppression of slow brain wave activity 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 50 sessions are usually required. The results of several controlled group studies indicate that EEG biofeedback may be effective in treating the core behavioral symptoms and may be 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 neurofeedback treatment and after complete discontinuation of stimulant treatment (225). 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 recently 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 (226). However, methodological questions remain regarding whether the actual agents of change are the biofeedback paradigm or the contextual factors (136).

Significant improvement of hyperactivity with Actigraph biofeedback has also been reported (227). The interactive metronome (228), 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 (228). Multisite studies are under way (228).

9.3.2. Elimination Diets

Based on the research of the last 20 years, it is difficult to dismiss summarily the findings that some children with ADHD respond favorably to individualized elimination diets (177). Behavioral improvement is more likely with appropriate elimination diets in individuals with atopic histories, a family history of migraine, and a family history of food reactivity (179); 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.

Supplements: Although pure Omega 3 supplementation has been shown not to affect ADHD (229), a recent double-blind, placebo-controlled study has shown that Omega 3:6-EFA supplementation improves manifestations of ADHD as well as improving reading and spelling in children with developmental coordination disorder, reading disorders, and associated ADHD symptoms, without affecting motor coordination (230; for review, see 231).

10. Prevention

Considering the vast implications of ADHD for the individual as well as for society, and the fact that a good deal is known regarding 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. 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 to 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 infant's 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 afterward, as recommended by the AAP, promoting social and physical activity, and providing parental and caretaker responsiveness, may not eliminate ADHD, but may provide the background for optimal emotional and cognitive development within the constraints of genetic predispositions, and may mitigate the risk for development of psychiatric comorbidities.

In the child who is at high risk for or who has manifested 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 (232). 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.

11. Conduct Disorder

Conduct disorder, as described in DSM-IV, is manifested by a repetitive and persistent pattern of behavior in which the basic rights of others or major age-appropriate societal norms or rules are violated. This comprises of 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.

11.1. Epidemiology

Three to 5% of preadolescent boys and 6 to 8% of adolescent boys meet criteria for conduct disorder. Boys outnumber girls 4:1 before adolescence and approximately 2:1 in adolescence (232). The Ontario Child Health Study indicated that, for ages 4 to 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 to 8% of the offender populations that have an early onset involving serious crime and continue into adulthood. Of adolescence-limited offenders, 25% continue their delinquent behavior into adulthood. These late starters may offend with peers but behave well in school and at home (233).

DSM-IV distinguishes between two specific types of conduct disorder. Childhood-onset type, in which there is onset of at least one criterion characteristic before 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 before 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.

11.2. Genetics

The Iowa Adoption cohorts have demonstrated that the degree of adoptee aggressiveness and conduct disorder has a significant genetic component. Cadoret et al. (234) 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 ADHD. 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 seemed 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 (235) 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 (235). 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.

11.3. Risk Factors

Several risk factors contribute to the outcome of conduct disorder (236). Genes, 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 (236).

There is a link between under arousal 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 (236).

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. Boys are more likely to be arrested for violent crimes; and girls for truancy, prostitution, running away, or underage drinking (233).

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 seems 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 (237).

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 (236).

Reading disorder may be associated with abnormal language processing within the left temporal cortex and has been linked to conduct disorder (236).

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 (236).

11.4. 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 (238).

11.5. Neurobiological Findings

Many previous brain imaging studies in adults with antisocial behavior have shown functional and morphologic brain abnormalities. Sterzer et al. (239) 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 with those in healthy 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. (240) compared regional brain volumes from magnetic resonance imaging scans from 10 youths with early onset conduct disorder and 10 healthy control subjects 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 control subjects, 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. (241) conducted a study to examine a community sample of 12 children with combined subtype ADHD (ages 8–12 years, seven with conduct disorder) and

19 healthy control subjects matched for age, sex, 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 with the control subjects. The results suggested ADHD and ADHD comorbid with conduct disorder have similar cerebellar morphology.

11.6. 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 for long enough to make a difference. Programs such as Head Start may help prevent delinquency in conduct disorder in preschool-aged children in whom poverty, perinatal complications, maternal attachment problems, temperamental traits, and parental education are risk factors. Such programs provide children with stimulation, and provide parents with education and parental support in crisis (238).

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 multisystemic therapy treats adolescents with conduct disorder in their psychosocial environment and family interventions (238). Augmentation of treatment is done by targeting social skills, conflict resolution, and anger management.

Children in the childhood-onset group of conduct disorders have a history of behavior problems early in development and are 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. The 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 (232).

11.6.1. Pharmacotherapy

Medications are recommended only for treatment of target symptoms and comorbid disorders. Mood stabilizers, typical and atypical antipsychotics, clonidine, and the stimulants have been found to be useful in the treatment of children and adolescents with conduct disorder. Findling et al. conducted an 8-week, open-label outpatient trial to determine the effectiveness and pharmacokinetics of quetiapine in aggressive children with conduct disorder. Their preliminary data suggested that aggressive children with conduct disorder may benefit from quetiapine (242).

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 (236).

Risperidone and MPH 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 is also used for its effect on reducing aggression and impulsivity (236).

Donovan et al. found divalproex to be an efficacious treatment for explosive temper and mood lability in conduct disorder (243).

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 (238). 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.

12. Summary

The explosion of neurobiological literature on 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, sex, 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 heritability that, however, is polygenic, with clinical expression strongly mediated by environmental and familial factors. ADHD and conduct disorder seem to be genetically distinct, whereas ODD evolves within the context of ADHD. ADHD demonstrates extremely high affiliations with other neurodevelopmental and mental disorders. Research in the last 10 years 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 usefulness 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 is simple and highly effective, and averts some of the most detrimental psychosocial effects that occur when ADHD is 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

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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, because 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. Treatments of these disorders, to date, are largely unexplored and often extrapolated from studies in adults. Research in both pharmacologic and psychotherapeutic treatment options need to be further addressed in children and adolescents suffering from mood disorders.

Keywords Adolescents · Bipolar disorder · Children · Major depressive disorder · Mood disorder

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 (1–3), these disorders can impair growth and development if not properly addressed. Mood disorders often interfere with family and peer relationships and educational performance (4–6). These youngsters are also at increased risk for substance abuse, legal difficulties, and hospitalizations (7–9). Depressed children and adolescents are at increased risk for both suicide attempts and completed suicides (10, 11). 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.

1. Diagnosing Mood Disorders in Children and Adolescents

The *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition, text revision (DSM-IV-TR) provides diagnostic criteria for each mood disorder. When applying these criteria to a patient, it is crucial to consider the age of the patient, because 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 (12).

1.1. Major Depressive Disorder

The DSM-IV-TR (13) characterizes a major depressive episode as having five or more of the following symptoms, all present during the same 2-week period, and that represent a change from previous levels of functioning: 1) depressed mood most of the day (can be irritable mood in children and adolescents); 2) markedly diminished interest or pleasure in all (or almost all) activities; 3) changes in appetite or weight change (which can include a failure to meet expected growth rates (14)); 4) insomnia or hypersomnia; 5) psychomotor agitation or retardation; 6) fatigue or loss of energy; 7) feelings of worthlessness or excessive or inappropriate guilt; 8) diminished ability to think or concentrate; and 9) recurrent thoughts of death.

These symptoms must not be caused by the effects of medication, alcohol or drug use, or a general medical condition. In addition, uncomplicated bereavement is specifically excluded from the diagnosis of major depressive disorder (MDD). 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 2 consecutive months (13).

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1.2. Dysthymic Disorder

Dysthymic disorder (DD) 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 1 year (13). 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.

1.3. Bipolar Disorders

Bipolar I disorder is defined by at least one manic or mixed episode. The DSM-IV-TR defines a manic episode as a distinct period of "abnormally and persistently elevated, expansive, or irritable mood" lasting at least 1 week (13). To be considered true episodes of mania, they should be severe enough to require hospitalization, cause marked impairment in functioning, or have psychotic features. At least three (or four if the mood is irritable rather than elevated or expansive) of the following symptoms must be present for a mood disturbance to be considered mania: 1) inflated self-esteem or grandiosity, 2) decreased need for sleep, 3) more talkativeness than usual or pressure to keep talking, 4) flight of ideas or racing thoughts, 5) distractibility, 6) increased goal-directed activity or psychomotor agitation, and 7) excessive involvement in pleasurable activities that have a high potential for painful consequences (13).

Bipolar II disorder is characterized by one or more major depressive episodes accompanied by at least one hypomanic episode: "a distinct period during which there is an abnormally and persistently elevated, expansive, or irritable mood that lasts at least four days" (13). 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 (12).

Cyclothymic disorder is a chronic and fluctuating mood disorder of milder clinical symptomatology and is characterized by "numerous periods of hypomanic and depressive symptoms" (13). 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 1 year and without a symptom-free interval longer than 2 months.

The diagnostic criteria for bipolar disorder used for adults may not always be reliable in diagnosing mania in children and adolescents (15). Unlike adults, children and adolescents often present with a delay in initial manic symptoms, or may actually begin with a subclinical presentation (8). 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 (16, 17). The establishment of more developmentally appropriate diagnostic criteria has been suggested to provide more validity (18).

2. Etiology, Pathogenesis, and Neurobiological Findings

2.1. Hormones

Several biological/hormonal factors have been implicated in the development of depression, i.e., growth hormone, cortisol, adrenocorticotropic hormone (ACTH), prolactin, thyroid hormones, and melatonin. In addition, differences in treatment responses to various medications with respect to age suggest that neurobiological mechanisms are involved in the course of the disease. However, the role such neurobiological factors play in the etiology of pediatric and adolescent mood disorders is 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) (19, 20). 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 (21).

Conversely, some studies in children (22) and adolescents (23, 24) 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 (25). However, other studies have failed to replicate this finding (26). One case–control study comparing 44 adolescents with major depression and 37 nondepressed control subjects found no differences in nocturnal growth hormone secretion. However, when subjects in the depression group were divided into suicidal and nonsuicidal groups, a significant blunting of nocturnal growth hormone secretion was present in the suicidal group compared with the nonsuicidal group (27).

Another study (28) examined the growth hormone response to GHRH in 82 depressed children compared with 55 control subjects, matched for age, sex, 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 that growth hormone may function as a "trait marker" for depressive disorders (28).

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 (29). 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 (30).

Studies of the HPA axis in depressed adults have found elevated cortisol levels (31). 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 and adolescents and nondepressed control subjects (32, 33). Ryan et al. (34) found lower cortisol levels in children suffering from early onset MDD compared with nondepressed control subjects after an infusion of L-5-hydroxytryptophan, a serotonin precursor, suggesting an abnormality in cortisol regulatory mechanisms in some depressed children and adolescents. Other studies found severely depressed and suicidal children and adolescents manifest cortisol hypersecretion (35, 36). Depressed preschool-aged children also had cortisol irregularities when subjected to separation or frustrating stimuli (37). 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 (38).

Corticotropin-releasing hormone (CRH) levels have also been an important area of study, because cortisol secretion abnormalities have been linked to alterations in endogenous CRH secretion (39). Studies in adults have consistently demonstrated elevated baseline cortisol levels and blunted corticotropin secretion after CRH infusion (40). However, a comparison of prepubertal children with MDD and nondepressed control subjects did not find significant differences in baseline or post-CRH stimulation levels of either cortisol or ACTH (40).

Pineal gland irregularities and prolactin secretion are also hypothesized to be altered in mood disorders. Studies in depressed adults found blunted prolactin secretion after administration of serotonin precursors and agonists (41). Studies of depressed children and adolescents found significantly greater nocturnal secretion of prolactin in children and adolescents with nonpsychotic depression than in control subjects (42). Waterman et al. (43) 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 control subjects (26).

Common thyroid abnormalities have been found in depressed adults, but many of these abnormalities did not result in overt thyroid disease (44). 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 (44). However, results of thyroid studies in depressed children and adolescents are inconclusive.

One study (45) 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 HPA axis. A similar study by the same group (46) explored thyroid function in depressed children and reported reduced basal T4, T3, and TSH values. 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 healthy control adolescents.

2.2. Melatonin

Currently, there are few studies on melatonin in major depression in youth, but several of these studies suggest that melatonin secretion may be altered in children and adolescents with primary major depression (47–49). A small study by Cavallo et al. (47) found lowered nocturnal serum melatonin levels in depressed boys, aged 7 to 13 years. Another study found that depressed children and adolescents produced higher levels of overnight urine melatonin than those without primary major depression (48). A study exploring pineal gland function by measuring serum melatonin levels during both wakefulness and sleep in depressed children and adolescents found that nocturnal serum melatonin levels were significantly increased in subjects with major depression, and also demonstrated a significantly higher melatonin profile in those subjects with co-occurring psychotic symptoms (49).

2.3. Neurochemical Findings

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 thought to be involved in mood disorders, because drugs that increase its levels reportedly induce depressive symptoms in nondepressed adults and exacerbate depressive symptoms in patients with depression (50). The exact role of acetylcholine in mood disorders in children and adolescents is still unclear.

Antidepressants seem to function by restoring regulation of dysregulated neurotransmitter systems in the brain (51). Although serotonergic system dysregulation is demonstrated across the lifespan in depression, the nature of these neurotransmitter dysregulations seem 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 (TCAs), which seem to be more effective in older populations (42).

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 (52). Depressive symptoms in bipolar disorder are hypothesized to be secondary to a larger decrease in pump activity and a resultant decrease in neurotransmitter release (52). Guanine nucleotide binding proteins (53) have also been postulated to play an important role in the molecular etiology of bipolar disorder (54). This hypothesis is based on the finding that lithium attenuates the functioning of G proteins and dampens the oscillatory system, functioning to stabilize mood (55).

2.4. Sleep Abnormalities

The correlation between sleep abnormalities and depression has been studied in both pediatric and adult populations. However, results vary with age. Depressed children and adolescents frequently report sleep disturbances (56), but, to date, electroencephalogram (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 (57). Studies of depressed adolescents have reported prolonged sleep latency, reduced REM latency, and decreased sleep, but no differences in delta sleep (56, 58–61). In addition, increased sleep changes in inpatient adolescents and in those with psychosis, suicidality, and endogenous MDD subtypes have been observed (58, 60, 62). A review of sleep studies of depressed children (42) found only one study that reported recordable sleep abnormalities in depressed children. This study reported only decreased REM latency and increased sleep latency in an inpatient sample (63).

2.5. Genetic Factors

2.5.1. Major Depressive Disorder

Depressed children and adolescents commonly have family members affected by mood disorders. In fact, the reported lifetime risk of MDD in children of depressed parents ranges from 15% (64) to 45% (65). Twin studies have supported the presence of a genetic factor in the etiology of depression. The concordance rates for depression were much higher in monozygotic (54%) versus dizygotic (24%) twins (66, 67). Recurrence and an early onset of symptoms have been suggested as characteristics most associated with familial risk (68). In fact, lifetime rates of mood disorders in first-degree relatives of depressed inpatient adolescents are significantly higher than in the general population (69). In addition, first-degree relatives of depressed suicidal adolescents may have increased lifetime rates of suicidal behavior (70). Several studies report that children of depressed parents are at high risk to develop depression, and have increased risk for other psychopathology, including anxiety and disruptive disorders (12).

Relatives of patients with bipolar disorder are also at risk for major depression, because relatives of bipolar probands have higher rates of unipolar depression as well as bipolar disorder (71). In addition, a familial relationship has been suggested between major depression and bipolar type II disorder. However, large-scale studies to explore this relationship are lacking, to date (68).

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 (72). There is evidence to suggest a genetic component to the development of major depression (73). However, recent studies suggest that environmental stressors may be an important factor in the development of depression in a genetically predispositioned individual (74–76).

2.5.2. Bipolar Disorder

With an estimated heritability of 85 to 89%, bipolar disorder has a strong genetic component (71). Family studies of adolescent-onset bipolar patients found bipolar disorder was increased among first-degree relatives (77). In addition, an early onset of disease predicts a higher prevalence of illness in family members (78).

Similar to unipolar depression, the genetic basis for bipolar disorder is likely to be the cumulative effect of many genes (79), which leave a person susceptible to environmental influences and stressors that 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 (79).

2.6. Structural Brain Abnormalities

2.6.1. Major Depressive Disorder

Imaging studies in depressed adults have found decreases in frontal lobe volume when compared with age- and sex-matched control subjects (80). In addition, reduced volumes of the putamen (81), the caudate nucleus (82), and the hippocampus (83) have been reported. Because the frontal lobe undergoes significant change and development throughout adolescence (84), it is reasonable to think that changes in frontal lobe volume also exist in early onset depression. Using magnetic resonance imaging (MRI), Steingard and colleagues (85) measured frontal lobe and lateral ventricular volume in children and adolescents hospitalized for depressive disorders. Frontal lobe volume was decreased and ventricular volume was increased in depressed subjects compared with nondepressed control subjects.

2.6.2. Bipolar Disorder

Structural differences have also been found in the central nervous system of young bipolar patients compared with healthy subjects. Botteron et al. (86) examined MRIs in ten manic children and adolescents and five psychiatrically healthy subjects. They found increased ventricular volume and subcortical changes in bipolar subjects. A second study examined MRI findings in 32 pediatric subjects with a diagnosis of bipolar disorder and 15 healthy control subjects (87). This study found decreased volumes of cortical matter in bipolar subjects when compared with healthy control subjects, particularly in the parietal and temporal lobes and areas involving attentional control, facial recognition, and verbal and declarative memory. Although these studies are limited by small samples, they suggest neuromorphometric differences between children and adolescents with bipolar disorder and psychiatrically healthy control subjects.

A recent study used functional MRI (fMRI) to compare 12 boys aged 9 to 18 years with a diagnosis of bipolar disorder and at least one parent with bipolar disorder with 10 age-and IQ-matched healthy male control subjects (88). The children and adolescents in this study with bipolar disorder seemed to have underlying abnormalities in the regulation of prefrontal–subcortical circuits.

3. Psychological Theories of Mood Disorders

3.1. Psychoanalytic Theory

The psychoanalytic theory proposed by Freud (89) and Abraham (90) suggests that depression is caused by the real or imaginary loss of a loved object. In turn, psychoanalytic theory suggests that mania is a reaction formation to depression, described as a defensive projection in which the patient focuses on the weaknesses of others to avoid thinking of his or her own weaknesses (91). Little scientific data are available to support this model for depression or mania, in part because of the arbitrariness of defining a loved object (12).

3.2. Learned Helplessness

Seligman and Peterson's (92) learned helplessness model theorizes that depression is connected to the experience of uncontrollable life events. These uncontrollable life events lead the person to perceive their 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.

3.3. Cognitive Models

Cognitive models provide a theory that account for the thoughts, or cognitions, associated with depression. In Beck's (93) model, distorted, negative thoughts characteristic of depressed individuals are seen as underlying depression.

3.4. 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 (91). 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 (94). Regarding mania, when child-rearing practices of manic parents were examined, many had parents with poor parenting techniques (95). 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 (15).

4. Epidemiology

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 MDD in prepubertal children, to date (12). In specialized populations, depression was reported in 7% of children admitted to pediatric hospitals for medical reasons (96) and in 40% of children in pediatric neurology clinics presenting with headaches (97). In prepubertal children, depression occurs at approximately the same rate in both sexes (3). However, after puberty, there is a marked difference in the sexes, with female patients presenting with major depression twice as frequently as male patients (1). 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 MDD in adults (98). An epidemiological study reported prevalence rates of DD of 1.6 to 8.0% in adolescents (99).

4.2. Bipolar Disorders

Bipolar disorder does not occur as often in the general population as MDD or DD. The lifetime prevalence of bipolar disorder approaches approximately 1% by adolescence (8). Geller et al. (100) reported the mean age of childhood onset bipolar disorder as approximately 8 years. Burke et al. (101) 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 (102–104). Children

and adolescents with bipolar disorder have a more prolonged course and have decreased response to treatment (9, 102).

5. Clinical Presentations and Phenomenology

5.1. Depressive Disorders

Young children, unable to express emotions like adults, present with more somatic complaints, psychomotor agitation, and mood-congruent hallucinations (12). 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 (105). It has been suggested that symptoms of "endogenicity"—melancholia, psychosis, suicide attempts, lethality of suicide attempts, and functional impairment—increase with age (1).

5.2. Bipolar Disorders

Bipolar disorder also presents with variability at different stages of development. Younger, preschool-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, and disordered sleep patterns, with high activity levels in the bedroom before sleep (106). 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 (107, 108). Irritable, unpredictable, and labile moods are common in adolescents and may be more common than euphoria in this age group (12).

6. Sex Differences in Mood Disorders

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 (3).

Biologically, several changes have been implicated in the sex differences observed in depressed adolescents; however, evidence-based literature in this area is very limited. One theory involves the increased oxytocin production observed in postpubertal females (109). Changes in hormones such as progesterone, estrogen, and cortisol have also been implicated in the differences observed between the sexes in depression. There is also evidence in the adult literature to suggest that the patient's sex may affect response to medications, specifically SSRIs (110), but, to date, studies in this area have been inconclusive (111) and largely unexplored in pediatric populations.

6.2. Bipolar Disorders

Sex differences in bipolar disorder are even less studied. To date, there is no evidence to suggest a sex difference in the development and treatment of bipolar disorder in children and adolescents. There is a difference between the sexes during manic onset in childhood. Prepubertal onset mania may be more common in boys than in girls, particularly in hospitalized patients (100).

7. Differential Diagnoses/Comorbidities

7.1. Major Depressive Disorder

The most frequent comorbid diagnoses with MDD are DD (30–80%), anxiety disorders (30–80%), disruptive disorders (10–80%), and substance abuse disorders (20–30%) (12). In general, comorbidities with MDD are associated with a more severe and persistent course of depression (1). Thus, it is important to assess comorbid psychiatric diagnoses because they may influence treatment and have an impact on the course of depression. Anxiety disorders coexist in a third of children and adolescents with MDD (112). The comorbidity of MDD and anxiety disorders can have important clinical implications because there may be an increased risk for substance abuse, suicidality, poor response to psychotherapy, and psychosocial problems (12). 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 (112).

Conduct disorders are also common in children. They may be present in 15 to 30% of depressed children and adolescents (113). More than 50% of children and adolescents with a mood disorder have conduct disorder or oppositional defiant disorder (12). Symptoms of conduct disorder such as irritability, oppositional defiance, and social withdrawal may mask MDD symptoms (112). Youth with both MDD and conduct disorders are at increased risk for suicide (114). Although comorbid conduct disorder and MDD in childhood is not associated with increased risk of MDD in adulthood (112, 115), 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 (12).

Substance abuse is also a common comorbid diagnosis in adolescents with MDD (1). Rao et al. (116) found that depressed adolescents had an earlier onset of substance use disorders and greater psychosocial impairment than control subjects.

Comorbid obsessive–compulsive disorder (OCD) occurs in 10 to 30% of children and adolescents with MDD. Severe OCD symptoms require treatment. However, they should be addressed after the treatment of the depressive symptoms, because mood disorders can interfere with a patient's motivation and compliance with behavioral therapy programs (112).

Several diagnoses included in the differential diagnosis of MDD should be excluded. For instance, adjustment disorder with depressed mood is a possibility in a school-aged child with a depressed affect. In this diagnosis, several depressive symptoms are present, but there are not enough symptoms present to warrant a diagnosis of MDD, and the duration is shorter than 6 months (91). Another important diagnostic consideration (especially in adolescents) is substance-induced mood disorder with depressive features. This diagnosis is made when the depressed mood is caused by the physiological side effects of a medication, drug of abuse, exposure to a toxin, or other somatic treatment (12). A substance-induced depression can be distinguished from a MDD by the onset, course, and clinical presentation of the disorder (116). It is also important to consider all medical conditions that may produce psychiatric syndromes similar to MDD or DD (91).

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 (15). Hyperthyroidism may present with a manic-like state (15). Neurological conditions such as head trauma, multiple sclerosis, stroke, and seizure disorders with a left temporal focus may also cause a manic syndrome (15). Space-occupying lesions, such as meningiomas, gliomas, and metastatic lesions in the thalamus, have been implicated (117).

Psychiatric disorders can also 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 (118). 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 (15). It has been suggested that childhood-onset bipolar disorder frequently is comorbid with ADHD (119).

Conduct disorder is also frequently comorbid with bipolar disorder (120). 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 (15). 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 (15).

Schizophrenia may also be confused as a manic episode because of the presence of delusions and hallucinations in both disorders (15). Psychotic symptoms are common in prepubertal manic children (106). Usually, the onset of schizophrenia is more insidious, and the onset of a manic episode is usually acute (15).

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 (12). Therefore, it is important to evaluate for sexual abuse and exposure to inappropriate adult sexual behaviors when considering the diagnosis of bipolar mania (117).

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 (14). Treatment setting is also a consideration. It must be determined whether the patient may be treated appropriately on an outpatient basis. Hospitalization may be required to protect the child or adolescent from either their own dangerous behaviors or to protect them 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 (121, 122). In general, treatment is currently based more on outpatient models.

8.1. Biological and Pharmacological Treatments

8.1.1. Major Depressive Disorder

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 aged 7 to 18 years, depending on the study (2, 123, 124); one randomized, controlled study of paroxetine, placebo, and imipramine in adolescents ages 12 to 18 years (125); one multicenter randomized, double-blind, placebo-controlled trial of sertraline in children and adolescents aged 6 to 17 years (126); a randomized, placebo-controlled trial of citalopram in children and adolescents aged 7 to 17 years (127), and one double-blind, randomized, placebo-controlled trial of escitalopram in children and

adolescents aged 6 to 17 years (128). With the exception of the escitalopram trial, which only demonstrated significant improvement in a post hoc analysis, all studies found statistically significant improvement in depressive symptoms when compared with placebo. Fluoxetine is currently the only SSRI approved by the US Food and Drug Administration (FDA) specifically to treat depression in children older than 8 years of age. Medications such as fluvoxamine have proven themselves safe and effective in treating other childhood disorders, i.e., OCD. 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 (129). There is little information regarding the impact of age on absorption, metabolism, therapeutic levels, or possible drug interactions of SSRIs. The relative dosage (milligrams per kilogram) may need to be higher to obtain similar serum levels in children as compared with adults (130).

The American Academy of Child and Adolescent Psychiatry (AACAP) guidelines recommend continued treatment with an SSRI for 6 to 12 months after clinical response (131). 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 (131).

Common side effects for SSRIs include gastrointestinal upset, decreased appetite, headache, restlessness, insomnia, and fatigue. These effects are usually dose-dependant and do not seem to be long term (132). Recently, concern regarding the use of SSRIs during pregnancy has been raised because of the development of persistent pulmonary hypertension of the newborn (PPHN) in infants exposed to SSRIs late in pregnancy (133). Additionally, congenital malformations, particularly ventricular septal defects, may be linked to SSRIs, particularly paroxetine (134).

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 (132). Although no individual trial demonstrated a statistically significant risk of suicidality, many trials had a relative risk of at least 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 (12).

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 (123). In this study of 439 adolescents aged 12 to 17 years, 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 (CBT) 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 (132).

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 to 14 years on antidepressant medication are at highest risk for conversion to a manic episode (135), but further suggests that children on SSRIs may be at lower risk for a manic switch compared with those on other antidepressants, such as TCAs. However, further analysis of this data suggests that prepubertal children (aged 5–14 years) are at higher risk of new-onset mania on SSRI treatment than older adolescents and adults (aged 15 to 29 years) (136). Other suggested risk factors for switching to a manic episode include family history of bipolar disorder and multigenerational mood disorders (132).

8.1.1.2. Tricyclic Antidepressants

TCAs, previously a mainstay of treatment for MDD, have been well studied and often used in adult patients. Studies of TCAs in adults with MDD have established their efficacy in acute (137) and maintenance treatment (138). Yet, literature reviews and a meta-analysis of 12 randomized controlled trials of TCAs in patients aged 6 to 18 years (139) have not supported efficacy in children and adolescents (122, 140, 141)

A literature search on the cardiovascular effects of TCAs in children and adolescents (142) found that 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 (143). The case fatality rate was significantly higher for children and adolescents on desipramine compared with all other TCAs. The authors recognize that the explanation for relatively higher rate of toxicity with desipramine

compared with the other studied TCAs is largely unclear. They do, however, suggest that pharmacodynamic factors may be implicated (143).

8.1.1.3. Monoamine Oxidase Inhibitors

Historically, monoamine oxidase inhibitors (MAOIs) have been a second-line treatment for depression in adults (144), but they may be more effective than TCAs for depression with atypical features, i.e., increased sleep, increased eating, and weight gain (145). However, the dietary limitations and risk of tyramine-induced interactions have limited their use in children and adolescents (146).

To date, there are few studies of MAOIs in adolescents. In a chart review, Ryan et al. (147) 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 (147). Newer MAOIs, such as moclobemide, have benefits over the older, nonselective MAOIs. First, they do not seem to impair cognitive function in young adults as do older antidepressants (148). This is a significant advantage for school-aged children. Second, these newer medications may not require the dietary restrictions of the older, nonselective inhibitors. Unfortunately, studies using these medications in depressed children and adolescents are still lacking (144). In general, these agents tend to be used in responsible adolescents with treatment-resistant depression.

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 (149). These side effects may worsen if bupropion is combined with other medications, such as fluoxetine. Concerns regarding seizures in bulimic adults 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 less than 450 mg/day in adults, seizures occur in approximately 4 in 1,000 patients (150). 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 (151).

Venlafaxine inhibits reuptake of both serotonin and norepinephrine from the synaptic cleft (152). Similar to SSRIs, venlafaxine lacks significant affinity for muscarinic, cholinergic, histaminic, or α_1-adrenergic receptors (12). Venlafaxine is one of the few newer antidepressants to have pharmacokinetic data for children and adolescents (153). However, a double-blind, placebo-controlled study of 33 depressed subjects aged 8 to 17 years did not find improvement of depressive symptoms (154). The authors of this study suggest that CBT, which was administered to all subjects, may have masked the effects of venlafaxine versus placebo.

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 (144). 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 years), nefazodone was generally well tolerated (140). 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.

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 CBT, particularly if there is a family history of depression found only to be responsive to ECT (12). 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.

8.1.3. Summary

With the relative lack of randomized controlled studies in children and adolescents with depression, there is debate regarding which pharmacotherapy is best for a depressed child or adolescent. The Texas Children's Medication Algorithm Project, established in 1999, (155) addressed this issue by creating a systematic approach to a treating a depressed child or adolescent. They suggest an SSRI, used cautiously, as a first-line treatment. This is followed by several other pharmacologic options, leading to the final consideration of ECT. However, these recommendations were proposed before the FDA warnings regarding SSRIs and antidepressants were initiated.

Regarding duration of pharmacotherapy, discontinuation could be considered 6 to 9 months after symptom resolution,

and medication should be gradually tapered (12). Unfortunately, little is known regarding the long-term pharmacological treatment of depression in children and adolescents. In particular, there are few studies of difficult to treat subpopulations, which have been excluded from research trials, i.e., those with suicidal thoughts, comorbid substance abuse, or other disorders. For these cases, clinicians must rely more heavily on clinical experience.

8.1.4. Psychotherapeutic Treatment Options

8.1.4.1. Major Depressive Disorder and Dysthymic Disorder

The psychotherapeutic treatment options available for children with MDD and DD 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 (91). A combination of various short-term therapeutic techniques may be the most efficacious treatment option for the child or adolescent with a depressive disorder (156).

Cognitive Behavioral Therapy. CBT is an effective treatment for depressed children and adolescents. It addresses the cognitive biases that maintain depression (12). CBT is based on the cognitive theory that individuals trigger and maintain depression by specific dysfunctional cognitive constructs (157). 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 (112).

A study comparing 12 to 16 weeks of individual CBT, nondirective supportive psychotherapy, and systematic behavior family therapy in a group of 107 clinically referred, depressed adolescents found that 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 (158). Wood et al. (159) 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.

TADS was a 12-week, multisite, double-blind, placebo-controlled study of 493 adolescents (aged 12–17 years) with a diagnosis of MDD. There were four treatment groups: 1) fluoxetine only, 2) CBT only, 3) CBT plus fluoxetine, and 4) placebo. The combination treatment group had a 71% response rate, compared with a 61% response rate for fluoxetine alone, a 43% response rate for CBT alone, and a 34.8% response for placebo. The combination of CBT and fluoxetine had a response rate twice that of placebo (123), which was a statistically significant difference. In addition, the combination of fluoxetine and CBT was superior to either fluoxetine alone ($P = 0.02$) or CBT alone ($P = 0.001$). As more studies are conducted on the efficacy of CBT, its effectiveness for the prevention of depression in a high-risk population (i.e., children of depressed parents) should be evaluated (160).

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 (161). 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 because of the difficulties of interacting with a depressed child or adolescent (162). 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 being conducted by Sanford et al. (163) on family psychoeducation (FPE) found that FPE influences processes that are thought to affect the course of adolescent depression. Its use increased parent–adolescent relationships and improved social functioning. FPE might have the potential to reduce recurrence of subsequent major depressive episodes.

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 (164). Fine et al. (165) compared two forms of short-term group therapy for depressed adolescents: a therapeutic support group and a social skills group. Subjects in the therapeutic support group shared common problems, developed new ways to cope with stressful situations, and provided mutual support. Subjects in the therapeutic support group improved significantly more than those in the social skills group. Adolescents treated in the therapeutic support group 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.

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 (12). 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 (166, 167). Mufson and Fairbanks (168) 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 ten depressed adolescents who participated in the follow-up evaluation, only one 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 (168). The positive results of this study provide support for additional research on IPT-A (12).

8.2. Bipolar Disorder

8.2.1. Pharmacotherapy

Few studies have been published regarding the pharmacotherapy of bipolar disorder in children and adolescents. Current guidelines suggest lithium or valproate may be used as first-line agents for nonpsychotic mania in pediatric bipolar patients (169).

8.2.1.1. Lithium

Lithium is the medication most studied in children and adolescents with bipolar disorder. It is currently the only FDA-approved mood stabilizer for children and adolescents older than 12 years of age (150). Support for lithium in children and adolescents with bipolar disorder comes from several case reports (170), open trials (171, 172), and one double-blind, placebo-controlled trial (173). It has been estimated that 40 to 50% of children and adolescents respond acutely to lithium monotherapy (174).

Lithium dosing is more complicated in children than in adults, because it is reported to have a shorter half-life and higher total clearance in children (175). The therapeutic range for lithium blood levels ranges from 0.6 to 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 (170) and a kinetics-based method (176). 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 (170). The kinetics-based model uses a single 600-mg lithium test dose to predict serum lithium levels in children (176).

Because of chronicity and unpredictability of symptoms in child and adolescent bipolar disorder, the optimal duration of antimanic treatment is difficult to establish (12). However, evidence supports long-term maintenance therapy with lithium, because discontinuation of lithium has been associated with an increased risk of relapse (9, 177). Furthermore, restabilizing patients on lithium once therapy has been discontinued or interrupted can be difficult (178, 179).

Children treated with lithium should carefully be monitored for adverse effects on the renal and thyroid systems. Serum electrolyte levels should be obtained at regular intervals (180, 181). Some studies of lithium found an association with cognitive impairment, including confusion and forgetfulness, at even low lithium plasma levels (182, 183). 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 gastrointestinal complaints (nausea and diarrhea) (172). Renal, ocular, thyroid, neurological, dermatological, and cardiovascular side effects are less common (12). In addition, there has been concern regarding lithium therapy in sexually active adolescent females, because this medication has been associated with various congenital abnormalities, particularly Ebstein's anomaly, a malformation of the tricuspid valve.

8.2.1.2. Anticonvulsants

Anticonvulsant medications have been used in the acute and prophylactic treatment of bipolar disorder in children and adolescents, particularly in the management of mixed states and rapid-cycling bipolar disorder (184, 185).

Valproate. Although valproate is commonly used in the acute treatment of children and adolescents with bipolar disorder, there are no double-blind, placebo-controlled studies to support its use. Valproate monotherapy had produced response rates of 53 to 80% in three open-label studies (186–188).

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 seems to occur almost exclusively in children younger than 2 years of age and is more common among those on a combination of anticonvulsants (189). The North American Antiepileptic Drug Pregnancy Registry suggests a 10.7% rate of major congenital malformations (compared with 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 (190). Valproate has also been associated with hyperammonemic encephalopathy (particularly in patients with urea cycle disorders) (191), benign thrombocytopenia (192), and weight gain (193, 194). Other side effects include sedation, nausea/vomiting, tremor, hyperglycemia, and alopecia (195).

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 years had polycystic ovaries or an elevated serum testosterone concentration, as compared with 27% of women taking other antiepileptics. Regarding women older than the age of 20 years, 56% of those on valproate had polycystic ovaries or elevated serum testosterone compared with 20% of those on other antiepileptics (196). Isojarvi et al. (197) found that the severity of this metabolic syndrome was reduced when valproate was replaced with lamotrigine in 16 women (suggesting a partial reversibility). The generalizability of these findings to psychiatric populations is unclear because current reports are confined to women with epilepsy (12).

Carbamazepine. 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 (198), no controlled studied have shown carbamazepine to be effective as monotherapy in children and adolescents with bipolar disorder.

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 (199). It was a safe and effective treatment for acute mania and long-term maintenance treatment in three patients with juvenile-onset bipolar I disorder (200). However, other studies did not find carbamazepine more effective than placebo (186).

Carbamazepine is usually initiated at a low dose and is adjusted up based on tolerability to achieve blood levels ranging from 6 to 12 μg/mL (201, 202). This typically corresponds to a maintenance dose of 10 to 20 mg/kg/day, given in divided doses, which could be as high as 1,200 mg/day in adolescents (203, 204). 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 that use the cytochrome P450 system (150).

There is currently a black box warning for carbamazepine, because it has the potential to cause blood dyscrasias (150). Aplastic anemia, agranulocytosis (205), and leukopenia (206) 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 girls, because relationships between carbamazepine and craniofacial defects, neural tube defects, and cardiac malformations have been reported (207). 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 (150).

Oxcarbazepine. Oxcarbazepine, an analog of carbamazepine, has a similar efficacy but has a lower risk of side effects. Thus, no blood level monitoring is required. Because oxcarbazepine is a weaker inducer of cytochrome P450, it does not have as great an effect on drug–drug interactions as carbamazepine (208). Cases studies support oxcarbazepine use in bipolar disorder in children and adolescents (209, 210), but there are, to date, no published controlled studies that support its use in this age range. Important adverse reactions reported with oxcarbazepine include drug-induced hyponatremia and dermatological/hypersensitivity reactions (211, 212). In addition, oxcarbazepine may reduce contraceptive efficacy by altering plasma estrogen concentrations. Thus, birth control options should be evaluated when treating bipolar female patients of child-bearing age (213).

Other Anticonvulsants. 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. Recent open-label trials found lamotrigine effective as a monotherapy (214, 215) or as an adjunctive treatment (216). However, an age-related association with Stevens–Johnson syndrome and other potentially life-threatening rashes (217) may limit its use in children and adolescents. Preliminary data of topiramate in bipolar youth found improvement of young mania rating scale (YMRS) scores, but this was not statistically significant (218). The possibility of decreased sodium bicarbonate levels, leading to hyperchloremic metabolic acidosis in youths treated with topiramate for seizure disorder, has been reported (219). Other possible adverse reactions from topiramate include impaired sweat production and cognitive impairment (220, 221).

8.2.1.3. Atypical Antipsychotics

Several case reports of children and adolescents who were unresponsive to other mood stabilizing medications found that clozapine was effective in alleviating manic symptoms (222–224). Furthermore, an open trial in hospitalized adolescents who had failed previous 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 (222, 223). Weekly blood draws are required when initiating treatment to monitor for clozapine-induced agranulocytosis. This may hinder widespread use in children and adolescents.

To date, there is one open-label study of olanzapine (225). Overall response rate was 61% in 23 children and adolescents, aged 5 to 14 years, with bipolar disorder. Mean weight gain in this study was 5 kg during 8 weeks of treatment. Common side effects of olanzapine are somnolence, agitation, and insomnia (226).

Double-blind, placebo-controlled studies of adults with bipolar disorder reported that risperidone was an effective treatment for acute mania (227, 228). There are no double-blind, placebo-controlled studies of risperidone for acute mania in children and adolescents. However, a recent open-label study of 22 children and adolescents found a 70% response rate after 8 weeks of treatment (229). A chart review of risperidone use in children and adolescents found an average weight gain of 1.2 kg/month, during 6 months (230).

A double-blind, placebo-controlled study of 30 hospitalized adolescents with either manic or mixed symptoms found that quetiapine was as an effective adjunctive treatment when added to divalproex therapy (231). Common side effects for quetiapine are somnolence, dizziness, dry mouth, elevated liver transaminases, and constipation (226).

All children and adolescents on atypical antipsychotics should be monitored for neuroleptic malignant syndrome, tardive dyskinesia, and weight gain. They should also be alerted to the potential development of metabolic syndrome. Ratzoni et al. (232) examined 50 Israeli adolescents on either risperidone (n = 21), olanzapine (n = 21), or haloperidol (n = 8). After 12 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 (232). Patients and their parents should be counseled regarding 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 (233).

8.2.2. Electroconvulsive Therapy

Electroconvulsive therapy (ECT) has been an effective treatment for acute mania in adults (234, 235). Studies in adolescents estimate a 75 to 100% response rate in mood disorders (236). However, ECT has been infrequently used, 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 (237). Current practice parameters suggest that 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 (236).

8.2.3. Treating Depression in Bipolar Children and Adolescents

Although the above treatment options focus mainly 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. This may require mood stabilization with the above-mentioned medications with supplemental antidepressants to address depressive symptoms. However, because antidepressants have been reported to elicit manic conversion, adequate mood stabilization should be achieved before initiating antidepressant therapy (132).

8.2.4. Psychotherapeutic Treatment Options

The practice guidelines for treatment of adult patients with bipolar disorder (234) list eight specific interventions that are essential for psychiatric management of bipolar disorder: 1) developing and maintaining rapport, 2) monitoring the patient's mood and behavior, 3) providing information and education about bipolar disorder, 4) enhancing compliance with medication and other treatments, 5) promoting regular patterns of sleep and daily activities, 6) promoting integration and adaptation to the psychosocial effects of bipolar disorder, 7) recognizing new episodes early on, and 8) minimizing the morbidity and academic, social, and interpersonal consequences of bipolar disorder. These same principles may be applied to treatment of bipolar disorder in children and adolescent, but differences in development should be taken into account. Psychosocial treatments are a mainstay of therapy between acute episodes and are aimed at reducing morbidity and preventing relapse. 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 interventions (146, 238).

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 under-recognized 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 MDD and DD 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. Genetic, hormonal, and physiologic influences have been implicated in the development and progression of mood disorders in adults. However, these pathways still need to be explored in children and adolescents.

Evidence for pharmacologic treatment for children and adolescents with depression is limited because of the lack of double-blind, placebo-controlled studies. However, treatment with SSRIs after informed consent is the current mainstay of treatment in this population. CBT, IPT, and group therapy adapted for use with younger patients may help adolescents with depression. Clinicians treating children and adolescents with bipolar disorder are also left with limited options. Current evidence suggests therapy with lithium or valproate is helpful. However, current studies of anticonvulsants and antipsychotic medications suggest they may be proven useful in the future. Most psychotherapeutic treatment guidelines for children and adolescents are based on guidelines established for adults with bipolar disorder.

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
Autistic Disorder

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Abstract This chapter identifies the biological underpinnings, phenomenology, assessment, and medical treatment of autism, 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. In addition, new assessment technologies have come on line to provide greater clarity in what collection of observations should be called autism and what would not. A more uniform approach to classification and diagnosis will facilitate a better understanding of treatment trial outcomes. Although interventions that alter the pathophysiological processes that are being identified are yet to be formulated, approaches to treatment that fail to take into account the 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 Assessment · Autism · Genetics · Histology · Neuronal proteins · Treatment

1. Introduction

Autism is a neurodevelopmental disorder whose conceptualization has had many transformations in the 60 years since it was first described in a small case series by Leo Kanner (1). The symptoms of the condition have been attributed to a myriad of causes, with outspoken advocates for both environmental and biological etiologies, most of which were found to be groundless when the scientific method was applied to test their validity. However, over time, a substantial body of empirical data has accumulated, which, at this point in our understanding of the disorder, defines the medical basis of autism. This chapter discusses that which can be tested and known. Unfortunately, much of the extant research studies have significant methodological limitations and available findings need further replication and refinement. A finer grained picture of current findings through larger and better-designed studies is needed. It is likely that new areas of inquiry, new investigative procedures and approaches, and cross discipline approaches will need to be considered. It is not clear how close the field is to merging all of the data so that a coherent testable theory can emerge and scientific resources be focused and better applied.

The direction of this chapter proceeds from identification to treatment, and covers the areas of epidemiology, genetics, comorbid disorders, brain findings, and both biological and educational/psychosocial treatments. Many of the points are made from a perspective of grounding the clinician in information to permit rational clinical decision making and to best direct care and inform caregivers of the many aspects of causes and treatments for the affected individuals. Its focus is autism and not all of the disorders that fall under the rubric of pervasive developmental disorders, each of which might be a focus of review in and of themselves.

2. Diagnostic Criteria, Assessment, and Measures

Variation in the quality and quantity of information applied to diagnostic algorithms can lead to low interrater reliability and diagnostic disagreements among practitioners. However, obtaining sufficient and specific information and firmly establishing the criteria on which a diagnosis is based can be crucial in improving diagnostic accuracy. The fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders*, text revision (DSM-IV-TR) (2) and the 10th revision of the *International Statistical Classification of Diseases* (ICD-10) (3) are the two standardized diagnostic systems currently in use for establishing a diagnosis and they have many similarities. Comparing the two systems, highlights some differences

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in the way the two taxonomies conceptualize disorders in the pervasive developmental disorders cluster. The pervasive developmental disorders in ICD-10 include Childhood Autism, Atypical Autism, Rett's Syndrome, Other Childhood Disintegrative Disorder, Overactive Disorder Associated with Mental Retardation and Stereotyped Movements, Asperger's Syndrome, Other Pervasive Developmental Disorders, and Pervasive Developmental Disorder, Unspecified. In DSM-IV-TR, the overarching category of Pervasive Developmental Disorders includes a more limited set of conditions, including Autistic Disorder, Rett's Disorder, Childhood Disintegrative Disorder, Asperger's Disorder, and Pervasive Developmental Disorder Not Otherwise Specified. As can be seen by its more numerous categories, ICD-10 exerts greater emphasis on differentiating clinically important phenotypic differences among the pervasive developmental disorders. However, the criteria for Autism in DSM-IV-TR (Table 20.1) and Childhood Autism in ICD-10 are conceptually very similar, but exhibit some very minor differences as well (4). Field tests have demonstrated that both diagnoses have high sensitivity and specificity (5). One such difference between these systems includes the disorders that must be excluded before the diagnosis of autism is made. The DSM-IV has a limited set to consider: Rett's Disorder or Childhood Disintegrative Disorder. ICD-10 is more extensive: 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. ICD-10 requires the diagnostician to consider and separate out non-autistic development in situations that share similar phenotypic features. For example, when language and social development are impaired but not all criteria for autism are satisfied, Pervasive Developmental Disorder Not Otherwise Specified might be an appropriate DSM-IV category. In the ICD-10 system, the number of cases assigned to Pervasive Developmental Disorder Not Otherwise Specified may be limited, because categories such as specific developmental disorder of receptive language with secondary socioemotional problems may be a better fit. Another difference is the way ICD-10 describes specific language symptoms and features compared with DSM-IV.

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. 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 that solicit information through responses to prescribed questions completed by a reporter informed about the patient's developmental history. Diagnostic reliability improves when methods of data collection are combined.

Among the various diagnostic instruments and structured interviews for children with Autism is the Autism Diagnostic Interview—Revised (ADI-R). This semistructured interview for caregivers of children with autistic features can be considered for children as young as 18 months (6). The ADI-R is particularly effective in differentiating children with autism

TABLE 20.1. DSM-IV-TR diagnostic criteria for autistic disorder.

A. A total of six (or more) items from (1), (2), and (3), with at least two from (1), and one each from (2) and (3):
  1. Qualitative impairment in social interaction, as manifested by at least two of the following:
    (a) Marked impairment in the use of multiple nonverbal behaviors such as eye-to-eye gaze, facial expression, body postures, and gestures to regulate social interaction
    (b) Failure to develop peer relationships appropriate to developmental level
    (c) A lack of spontaneous seeking to share enjoyment, interests, or achievements with other people (e.g., by a lack of showing, bringing, or pointing out objects of interest)
    (d) Lack of social or emotional reciprocity
  2. Qualitative impairments in communication as manifested by at least one of the following:
    (a) Delay in, or total lack of, the development of spoken language (not accompanied by an attempt to compensate through alternative modes of communication such as gesture or mime)
    (b) In individuals with adequate speech, marked impairment in the ability to initiate or sustain a conversation with others
    (c) Stereotyped and repetitive use of language or idiosyncratic language
    (d) Lack of varied, spontaneous make-believe play or social imitative play appropriate to developmental level
  3. Restricted, repetitive, and stereotyped patterns of behavior, interests, and activities as manifested by at least one of the following:
    (a) Encompassing preoccupation with one or more stereotyped and restricted patterns of interest that is abnormal either in intensity or focus
    (b) Apparently inflexible adherence to specific, nonfunctional routines or rituals
    (c) Stereotyped and repetitive motor mannerisms (e.g., hand or finger flapping or twisting, or complex whole body movements)
    (d) Persistent preoccupation with parts of objects
B. Delays or abnormal functioning in at least one of the following areas, with onset before age 3 years: 1) social interaction, 2) language as used in social communication, or 3) symbolic or imaginative play
C. The disturbance is not better accounted for by Rett's Disorder or Childhood Disintegrative Disorder

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from patients with mental retardation and language impairment (7). Another instrument, which became the standard research method for establishing a diagnosis, has made its way into the clinic. The Autism Diagnostic Observation Schedule (ADOS) is a semistructured standardized assessment 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 administer the instrument. 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 30-minute modules, designed to accommodate the expressive language abilities of the child to be tested (8). The ADOS is not suitable for adolescents with severe or profound mental retardation (9). 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 with the autistic disorder, although changes in diagnostic criteria over time and a decrease in emphasis on sensory characteristics limits its current applicability (10–12). The Childhood Autism Rating Scale (CARS) is another older instrument that is valuable for screening and diagnosing autism. The instrument organizes the practitioner's interactions with the patient and rates the child's response, which is then compared with norms for normally developing children, children with mental retardation, and children with the disorder, against several subscales. Convergent validity studies have been conducted with findings of high agreement between DSM-IV and CARS (13). Finally, newer instruments, the Gilliam Autism Rating Scale (14) and the Parent Interview for Autism (15) are parent-rated instruments that have been found to be helpful and are becoming widely disseminated for screening and diagnostic purposes.

2.1. Assessment Instruments

Beyond diagnostic assessment, other domains of functioning, such as communication, intellectual capacity, and special sensory and neurological status, as well as consideration of a genetic evaluation need to be assessed as part of a core evaluation. Intellectual disability is a common comorbid feature of autism. Administering a measure of cognitive functioning and adaptive ability should be a routine part of an initial evaluation. Cognitive ability is an important predictor of outcome and is a useful guide for educational planning. The Leiter International Performance Scales—Revised is useful, especially when language skills are very deficient (16).

Language functioning, one of the main features of the disorder, should also be assessed with an eye toward prognosis and planning for the future. Pragmatic language, i.e., communication in the context of a social interaction, should be assessed, because 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 (17) is one instrument that may be suitable for this purpose.

Finally, level of adaptive ability may round out the initial evaluation. In cases in which intellectual functioning is below the 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 (18).

As will be clearer after the Sects. 3 and 4 on genetics and comorbid disorders, assessment for newly diagnosed cases should include DNA testing for fragile X, Williams, and Angelman syndromes with fluorescent in situ hybridization (FISH) testing. Testing to exclude 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, dihydropyridine dehydrogenase, adenylosuccinate lyase, and 5′-nucleotidase. Another laboratory measure to be considered in cases in which there is a history of pica, is lead level. The consequences of early lead intoxication on central nervous system (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 exam in older children should be considered.

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 (19). 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 one study (20–22). Although heritability estimates suggest that 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 (23). Analysis of family genetic studies estimate that up to 10 interacting genes contribute to susceptibility to autism (24).

The pursuit of specific susceptibility genes for autism has a long history of promise, but it 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 in which vulnerability conveyed by particular alleles may be common in the general population. Susceptibility genes have included loci on 2q, 7q, and 13q chromosomes (25–27). A recent genome-wide screen of multiplex autistic families

showed a number of chromosome regions with LOD scores at least 1.5, although none reached statistical significance. Loci included 3p25, 6q23, 12p12, 16p12-p13, 17q11.2, 17q21, and 19q13. Of these, 17q and 19p received the most support (28). The 19p locus seems 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 this loci (29–31). McCauley et al. also identified the 17q11.2 locus, which is a popular candidate locus in psychiatric disorders and, purportedly, may contain a gene for coding of the serotonin transporter protein (28). Another recent genome screen has also implicated this site (26).

One of the disorders of pervasive development has a very specific genetic cause. Rett's syndrome has been linked to a mutation at the MECP2 locus on the X chromosome. The condition is only found in female patients because female patients have two X chromosomes, one of which is normal. However, in the male fetus, that is not the case, and one copy of the MECP2 locus is lethal, with the fetus not coming to term (32).

Rather than approach autism as a genetically homogenous disorder, a research strategy that considers each domain of the disorder to have its own sources of genetic variability might prove useful in identifying putative genetic loci. Language impairment is one of the hallmarks of the disorder. Research with individuals with language disorders 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 (33). A recent study showed that loci implicated in specific language impairment overlapped with loci from an autism sample. Sites on chromosome 13q21 and at 7q31 for both conditions were identified (34). This approach seems to confirm the relevance of using candidate genes from disorders with related dysfunction as potential sites for investigation for similar phenotypic expression in autism. Another approach is to identify endophenotypes (35) and seek genetic linkages to these underlying biological foundations of the disorder. Possible choices might be phrase speech delay, seizure disorder, hyperserotonemia, eye contact, 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 codes for its expression. The delay in the acquisition of phrase speech, which may be governed by the 7q31 loci, is an example of an endophenotype with a putative genetic locus.

4. Comorbid Medical Disorders and Autism

The prevalence of various comorbid medical and neurodevelopmental conditions in autism is approximately 10%, but with a much higher rate in autism if associated with profound cognitive delays (36). Although this rate of comorbidity may seem high, it is still lower than, for example, the comorbidity rate for attention-deficit hyperactivity disorder. More interesting, perhaps, is the increased rate of some neurodevelopmental disorders comorbid with autism than their population rates unassociated with autism. This being the case, the possible common genetic links between the disorders becomes intriguing to explore; especially because specific genetic loci have been associated with a subgroup of neurodevelopmental disorders. In some of these disorders with known genetic basis, a co-occurring phenotype with similarities to autism can be found. These developmental disorders are well described both phenotypically and genotypically, so that their association with autism speaks for the possibility of chromosomal loci that may be relevant to autism. Prader–Willi and Angelman syndromes, as well as Fragile X syndrome (37) and tuberous sclerosis (38) fall into this category. Both Prader–Willi and Angelman syndromes have known chromosomal abnormalities at 15q11-q13. That site may be an important candidate locus for understanding one genetic vulnerability to autism (39, 40).

Fragile X Syndrome is the most common form of mental retardation, affecting approximately 1 in 4,000 male individuals and 1 in 8,000 female individuals (41, 42). Fragile X is caused by an instability of a portion of the X chromosome caused by an expansion of a three-nucleotide repeat, CGG. Approximately 15 to 25% of individuals with Fragile X syndrome also have autistic disorder (43, 44). On the other hand, the prevalence of autism with Fragile X syndrome is only 2 to 5% (45–47). A workup for autism in a group of patients with Fragile X will turn up a number of autism cases that previously were not identified. A genetic test for the Fragile X gene abnormality in a group of individuals with autism will turn up a small number, but results will have implications for genetic counseling among relatives.

Another disorder in which 25 to 60% of affected individuals have significant autistic traits is tuberous sclerosis. Tuberous sclerosis is an autosomal dominant disorder characterized by the classic triad of mental retardation, epilepsy, and skin lesions (48). The co-occurrence of autism spectrum disorder and tuberous sclerosis has been recognized for decades, with the prevalence of tuberous sclerosis in autism spectrum disorder estimated to be approximately 1 to 4% (49). The features of autism spectrum disorder are present in 20 to 25% of the individuals with tuberous sclerosis (50, 51). The genetic characteristics of this disorder is very interesting in that a similar phenotype is expressed by two separate genes, each of which contributes to approximately half of the cases. One of the sites is found on chromosome 16 and one on chromosome 9 (50). Awareness of the relationship between these two disorders is important during the assessment of individuals with either disorder.

The incidence of Down syndrome in children with autism is estimated to be as high as 11% (52, 53). Down syndrome is caused by three copies of chromosome 21, trisomy 21,

or the less common cause of Down syndrome, the translocation of a part of chromosome 21 to another chromosome. Because of the prominent physical features and delays and for reasons that may have to do with the system of care for Down syndrome, children with autistic comorbidity may be overlooked or the diagnosis is not made until the child is older (54).

Autistic patients have more than a 100-fold increased risk of developing neurofibromatosis 1 (NF1) as compared with the general population (55, 56). Also known as von Recklinghausen neurofibromatosis, it is identifiable by multiple *cafe au lait* spots and neurofibromas on or under the skin. Neurofibroma tumors may develop in the brain. Approximately 50% of people with NF1 also have learning disabilities. Multiple reports link the *NF1* gene and autism (55, 57).

A less well-known disorder that can present with autistic traits is 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, and heart defects and murmurs. In most cases, the affected individual is socially connected but some cases also present behavioral components associated with autistic features. The genetic etiology of this syndrome is an interstitial microdeletion at chromosome 17p11.2 (58). Prader–Willi, Angelman, Fragile X, and Down syndrome, and tuberous sclerosis may provide clues to the multifocal genetic sites that may contribute to the autistic phenotype. In addition to the implications for the pursuit of causal gene loci in autism, comorbid conditions have 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 autistic comorbidity. For the clinician serving patients with autism, a referral for genetic testing should be considered when a patient with autism has dysmorphic features or unusual physical and developmental trajectories that are not typical for autism.

5. Special Sensory Disorders and Autism

The presence of autism in congenitally blind children has long been a source of interest. The features of autism, including social deficits, stereotypies, and narrow range of interests, are strikingly common in some cases of congenital blindness (59–62). Special services and preventing sensory deprivation and social isolation are important treatment goals.

Comorbidity between autism and deafness has been well documented in the literature (63–65). One study looked at the hearing of a group of 199 children and adolescents with autism; mild to moderate hearing loss was present in 7.9% of these children (66). Autism can be difficult to diagnose in the presence of profound deafness. The clinician will be faced with difficult questions: Does the deafness explain the social isolation and communication deficits? Are these features better attributed to a pervasive developmental disorder, namely autism?

6. Neuroimaging Findings

Autism is a neurodevelopmental disorder affecting CNS functioning. Finding consistent differences in brain structures between affected and unaffected individuals should be evidence for this perspective and provide a better understanding based on location and extent of the anatomical differences that account for the symptomatology associated with the disorder. Many studies have pursued this direction. One of the most replicated neuroanatomical findings is large brain volumes. This phenomenon has been refined in several studies to show that the volume increases in cerebral white and gray matter in early childhood compared with unaffected children, and is reversed in adolescence, leading to smaller volumes (67–70). Abnormally reduced volume in specific cerebellar sites has also been reported (71). The picture for a neuroanatomical signature for the disorder has hardly emerged however. Evidence for similar neuroanatomical cerebral volumes, i.e., low cerebral white matter volumes between monozygotic twins discordant for the narrowly defined disorder, suggests that we need to consider additional hypotheses in conjunction with neuroanatomical findings and to support a spectrum of phenotypic expression despite neuroanatomical commonalities (72). Other neuroanatomical findings that are relevant in understanding the disorder include poor connectivity at the temporoparietal junction (73). Decreased grey matter volume in the right paracingulate sulcus, the left occipitotemporal cortex, and the left inferior frontal sulcus were found in a well-controlled magnetic resonance imaging (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 (74).

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 social perspective-taking task was administered to high-functioning individuals with autism spectrum disorder. The task required the participant to make choices based on the ability of the subject to appreciate the emotional and cognitive position of others. Differences from control subjects would help elucidate some of the brain specific areas that are responsible for the social deficits of the disorder. A task was presented that required taking the perspective of another, while brain activity was imaged with positron emission tomography (PET). The area of the brain that was active for control subjects, the anterior cingulate and the medial frontal cortex, was less active in the affected group (75). 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 pathology in areas of the brain that regulate these frontal structures are two possible research directions to pursue.

7. Histopathology

Imaging procedures have been useful in elucidating both the sources of and the relationship between symptomatic dysfunction and anatomical correlates in autism. A finer-grained approach to the autistic disorder is led by investigators that use 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 (76–78). One of the earliest of histological abnormalities identified showed reduced numbers of Purkinje cells in the cerebellum. These large cells were found to be decreased in number or atrophic (77, 79). The areas most affected are the posterolateral neocerebellar cortex and adjacent archicerebellar cortex of the cerebellar hemispheres (80). Other areas of the brain were also shown to have abnormalities in neuronal configuration, size, or density. The hippocampus, subiculum, entorhinal cortex, amygdala, mamillary body and medial septal nucleus, and the anterior cingulate gyrus showed reduced cell size and increased cell density (77). Because many of the structures on this list are part of the limbic system, a possible brain–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 the autistic disorder.

7.1. Bauman and Kemper's Work

The early histological postmortem work of Bauman and Kemper might be seen as the foundation for the field's understanding of the medical basis of autism (81). Their detailed findings noted specific abnormalities in the limbic system and the cerebellum (77). Their work has included special staining of the pyramidal neurons in the hippocampus that showed decreased complexity and extent of dendritic arbors in these cells in this region (82). 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 (83). Additional evidence for abnormal neuronal cerebral cortical abnormalities comes from Casanova (84), who found increased numbers of cortical minicolumns that were smaller and more compact than in control subjects. Systematic histopathological examination by Bauman and Kemper (85) 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 implications beyond that of brain–behavior correlations. They have taken their data and considered its implications for time of onset of the presumed CNS insult and the dynamic nature of the pathological process. They have reported changing patterns of neuropathology from childhood to adulthood. For example, they found that neurons in the nucleus of the diagonal band of Broca of the septum were unusually large but of adequate numbers in children younger 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 (86). This could suggest an ongoing rather than a single-strike pathophysiological process. Another example of developmental changes that could suggest an ongoing neuropathologic process is the differences found in the cerebellum in the fastigial, globose and emboliform nuclei in the roof of the cerebellum. In the brains of children younger than 13 years old 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 (77,87). Finally, in keeping with a possible process of ongoing abnormalities are brainstem neuronal changes, in the inferior olive, 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 number. Retrograde atrophy can only be a factor if the connection between the two neuron groups was established, and this occurs early in pregnancy. Thus, the connection between Purkinje and olivary neurons may not have been established, leading to the preservation of the olivary neurons. This connection is solidified after approximately 28 to 30 weeks of gestation. Some unknown process before the fetus reaches 28 to 30 weeks of age may have been in place to cause this kind of neurological outcome (88). Altogether, histological changes that have their impact early in neonatal life as well as changes that seem to be ongoing through development defy a known neuropathological disorder. Illumination of a genetic, environmental, infectious, or other etiologic process awaits further study (88).

7.2. 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 a group of neuronal proteins around which the brain organizes the placement and viability of neurons would be a good starting point to determine whether the density or location of these trophic molecules may explain known brain abnormalities. This approach may be useful in explaining histopathological findings. Support for trophic factors being important in cytoarchitectural abnormalities can be found in the works of

Casanova (84) and Bailey (83). In addition, differences in these substances in the brains of autistic individuals compared with control subjects may support brain–behavior correlations. Fatemi et al., in 2001, examined the quantity of an antiapoptotic protein, Bcl-2, in an area that had been identified previously as containing fewer neurons in autism. It had been shown that autistic individuals exhibit 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 levels in the brains of adults diagnosed with autism that fell below the mean Bcl-2 levels in control subjects. In humans, the amount of Bcl-2 protein naturally varies over the life span. Understanding these variations allows determination of whether decreases at critical points in development may increase the risk of atrophy in 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 (89). This study remains to be done. In a related finding, this laboratory reported an increase in p53 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 (90). The abnormal ratio of expression of Bcl-2 controlling cell proliferation to p53 involved in apoptosis indicates a greater potential for cell death in the autistic brain secondary to various cell regulating influences (91). Because 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. Several known brain trophic factors have been investigated, including Reelin and gamma aminobutyric acid (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 (92). An animal model for understanding the function of reelin exists. The Reeler mouse has a genetic makeup containing a 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 autistic human. However, viral infection in the midterm pregnant mouse also showed reduction in reelin levels with similar abnormal cortical architecture in the offspring (93). In humans, a relationship has been found between a specific polymorphism of the Reelin gene and affected individuals with autism (94). 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 (95) and in the frontal region (92), but also demonstrated a significant reduction in one component of blood Reelin, the 410-kDa species, not only in the affected individuals but also in all parents and normal unaffected siblings (96). Reelin has been mapped to chromosome 7. As described above, Reelin has important implications for the integrity of neuronal cytoarchitecture in places in the brain that have been shown to be histologically abnormal. In addition, reduced circulating levels of Reelin have been found in 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 protein for future study.

Reports of abnormalities of the glutamate (increased) and GABA (decreased) system have been reported by several groups (97, 98). Possible related findings include a reduction in the rate-limiting enzyme, glutamic acid decarboxylase (GAD), which is responsible for normal conversion of glutamate to GABA. Fatemi et al. (99) showed that two isoforms of GAD, the 65- and 67-kDa proteins, GAD65 and GAD67, respectively, were reduced in two important brain areas of the autistic brain, namely the cerebellar and the parietal cortices. A decrease in GAD is likely to decrease the amount of GABA, which serves an inhibitory function in the brain, and therefore, cause an increase in glutamate, which is an excitatory amino acid. The clinical implications of this may be in the increased rate of seizures and heightened sensory arousal systems that are problematic in this disorder. GAD67 messenger RNA (mRNA) has recently been reported to be significantly reduced in autistic brains, supporting the abovementioned studies (100).

Receptors are a group of complex cellular substructures that would be of interest to examine for distribution and density in autism. Drawing a connection between brain regions that subserve specific functions, disordered neuronal histology and subcellular molecular anatomy would provide a link between these important levels of analysis. The significance of each level of analysis would add to our understanding of the expression of the disorder. Understanding of the functional MRI and neurocytohistological findings may rest on a coherent synthesis of this body of subcellular work. As noted in the works of Bauman and Kemper and others, the neurons of the hippocampus are abnormal. Blatt showed that the numbers of GABA receptors in the hippocampi of four autistic adults were reduced (101).

As intriguing as these findings are, they need to be reliably replicated in other research laboratories for their results to be trusted. In addition, how neuroregulatory proteins may themselves be regulated by either or both environmental and other genetic factors awaits continued research exploration. The current research in neuroregulatory proteins may elucidate the sought-for mediating steps between genetics, environment, and neuronal distortions in the pathogenesis of the autistic syndrome.

8. Immunological Abnormalities

Although abnormal neuronal architecture seems to be 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 through a mechanism that subsequently has an effect on CNS histology. For example, a genetic predisposition to a particular type of viral infection may set in motion 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 factors or environmental toxins act to produce the CNS disorder. Vargas et al. (102) noted that microglia and astroglia seem to be activated in the brains of autistic individuals in ways that were suggestive of an immunological response. Pliopys et al. (103) showed that antibodies directed at endothelial cells, neurofilaments, and myelin basic protein can be found in autism. Supporting evidence for immunological activation was presented by Ahlsen et al. (104), who also showed an increase in the level of glial fibrillary acidic protein, a marker of glial activation, in the cerebrospinal fluid and in the superior frontal, parietal, and cerebellar cortices of autistic subjects (105). The immune response to viral infection has been proposed to result in antibody production to neurotransmitter receptors, such as serotonin binding sites (106). Exposure to a virus prenatally may trigger an immunological response. Animal models with strategically timed exposure to common viruses have resulted in social deficits (107). Further evidence for susceptibility to viruses caused by impaired immune function is present but is sketchy in its depth. The reduction of natural killer cell cytotoxicity in autism is a 20-year-old finding (108). This was confirmed subsequently by Gupta (109), who also found lower levels of IL2, and IFN-γ. It is intriguing to consider a genetic predisposition to poor immunological functioning that facilitates viral infections, resulting in altered brain neurotropic factors, leading finally to the disorder. Such links between separate domains of study will necessitate interdisciplinary efforts to weave a coherent evidence-based pathophysiological etiology.

9. Electroencephalography

9.1. Seizures and Electroencephalography

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 autism spectrum disorders, occurring in approximately 20 to 30% of patients (110), and often present by adolescence. An even larger segment of patients with autism spectrum disorders have abnormal brain electrical patterns. Electroencephalogram (EEG) abnormalities are present in 8 to 72% of this population (110–115). Various studies have shown that the most frequent sites of the epileptiform abnormalities are localized over the temporal and frontal regions (112,113,116). 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 (112, 116). This lack of anatomical and electroencephalopathic specificity reduces the diagnostic role of electroencephalography as a screening or clinical tool in the assessment of autism spectrum disorder. The implications of the presence of seizures in the disorder are not clear. Approximately one third of autistic children undergo a regression, after what seems to be a fairly healthy developmental start, related to their language, communication, and behavior (114). However, this may not be associated with EEG changes. There are conflicting results linking autistic regression, epilepsy, and EEG abnormalities (114,117). Alternative thinking points to seizures more clearly being related to mental retardation rather than autism, with a significant association between mental retardation and epilepsy in this population (117). Finally, one possible research finding explaining the high seizure rate in individuals with autism is the decreased production of GABA (99, 100). GABA is an important inhibitory neurochemical in the CNS.

10. Epidemiology

The frequency of the disorder seems to be changing, and the causes range from increased case finding to environmental toxins. A recent estimate of prevalence for the spectrum of autism related disorders was reported as 34 in 10,000 (118). An epidemiological survey for the more narrowly defined autism phenotype suggested a prevalence rate of 10 per 10,000 (119). This compares to a prevalence rate 25 years ago of 4 to 6 per 10,000 (120). The most recent estimates of prevalence come from a review of epidemiological surveys that summarized approximately 40 years worth of research in this area. That review presented prevalence estimates by subcategories of the disorder. The diagnostic category of pervasive developmental disorder as now defined by DSM-IV contains disorders of very low rates, such as childhood disintegrative syndrome, with an estimate of 0.2 per 10,000 and Rett's syndrome, of 1 per 10,000, whereas Asperger syndrome and strictly defined autism may be 2.5 and 10 per 10,000, respectively (121). Two population surveys conducted by the Centers for Disease Control and Prevention (CDC) reported the prevalence of combined disorders of autism, Asperger syndrome, and pervasive developmental disorder not otherwise specified as 3.4 and 6.7 per 1,000 children (122). The CDC also conducted two nationally representative surveys of parents, the National Health Interview Survey (NHIS) and the National Survey of Children's Health (NSCH), and were able to estimate the population-based prevalence of parental report of diagnosed autism in the United States. They determined the prevalence of parent-reported diagnosis of autism was 5.7 per

1,000 children in NHIS and 5.5 per 1,000 children in NSCH (123). These reports suggest that rates are now higher, perhaps 10 times what were reported several decades ago. The most likely explanations for the apparent increase are improved case finding and the expanded diagnostic criteria for pervasive developmental disorder, as currently diagnostically defined (124, 125). However, causes that are more pernicious with significant public health implications are part of a very heated public controversy.

11. Putative Causes of Increasing Prevalence of Autism

Several causes of the observed increase in the prevalence of autism have been postulated. Some of the causes are speculated to be iatrogenic. These physician-attributed agents are thought to be toxic in some children and include vaccines or the thimerosal that is used as a preservative in the multidose vials of vaccine. Support for this hypothesis was generated by the alarming observation of significant developmental regression in some children soon after immunization with the measles, mumps, and rubella (MMR) vaccine (126–128).

The pathophysiological trail from these potential vectors to their connection to autism is not direct. One starting point begins with the speculation that the higher than expected incidence of diarrhea in this population may be part of or causative of autism. Several studies have implicated gut problems, faulty digestion, and the mitogens that are subsequently produced as a particular pathway leading to autism (129,130). However, because measles antigen has been isolated in gut biopsies from some of these cases, a connection was drawn between the inoculation, gut problems, and the neurodevelopmental consequences, namely autism (131–133). Other studies showed that the presence of intestinal abnormalities is not specifically associated with the measles antigen (134,135). Which is the cause and which is the effect is not entirely clear because the presence of apparent viral antigens could be a result of a gastrointestinal immunological disorder rather than its cause (134). More definitively, however, studies that have compared rates of autism in immunized and control subjects have detected no relationship of immunization to autism (136, 137).

If not the measles antigen itself, perhaps something associated with the immunization has some causative relationship to autism. A contentious argument has been made for the antibacterial agent contained in the multidose vial that is used for distribution. Thimerosal is a mercury-derived ethyl-bonded compound. What is described about thimerosal is often extrapolated from the methyl version. The pharmacodynamics of these two compounds are very different, which is reflected in their excretion rates. There is much work done on the toxicology of the methyl-bound compound that clearly demonstrates its toxicity in mammalian species. It is not clear that the ethyl compound is equally toxic because it is rapidly eliminated in the stool. In addition, blood levels of ethyl mercury in recently inoculated infants has been shown to be low (138). One of the strong proponents for the role of thimerosal in increasing the prevalence of autism is Geier et al. (139). In a report to the Vaccine Adverse Events reporting system of the CDC, they showed that the risks for neurodevelopmental disorders were increased by between 2.2- and 6-fold in children receiving the thimerosal-preserved diphtheria, tetanus, and pertussis vaccine (139). However, several studies have shown that rates of autism did not change even when thimerosal was removed from the vaccine (140), and several epidemiological studies comparing rates with and without thimerosal failed to confirm the association (141–143). It is unlikely that the threat of environmental toxins as a cause of autism will end with clarification of the thimerosal controversy. It may be necessary for a clearer understanding of genetic and biologic vulnerabilities to emerge through further research to allay parents' fears.

12. Treatment

Interventions for autism need to be as eclectic and disparate as the multiple features of the disorder. Intellectual impairment, language and social deficits, and behavioral problems need to be considered in treatment planning. Comprehensive treatment plans can 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 for their child with autism, including those that are medically oriented, such as treatment for comorbid psychiatric disorders, such as ADHD, OCD and depressive disorders, seizures, sleep problems, and restricted range of food choices leading to nutritional concerns and gut issues such as diarrhea and constipation. There are behaviorally oriented questions from parents, such as strategies for managing self-injury, inconsistent sensory reactions, aggression, destructiveness, and sexual behaviors. In addition, there are service-related questions, such the adequacy and type of school services, and advice and assistance in accessing mental health support and related services. And, finally, questions that impact the family, such as concerns about the impact of the affected child on siblings and family functioning and the personal and financial dilemmas involved with out-of-home placement. Clearly, the physician must be well versed in a variety of treatment approaches as well as the resources of the local child-caring systems, including school, mental and physical health, social service, and child welfare services, 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 autism can be found in reports by interested professional groups, including the American Academy of Child and Adolescent Psychiatry (144).

The perspective toward treatment for autism, as it is for all child mental disorders, is developmentally based. Creating developmental progress in a child with autism involves accurate assessment of baseline abilities, marshalling of the resources of family and community, picking targets of treatment with functional outcomes, and estimating the probability of response to intervention. Indicators of response to treatment are poorly understood. In some cases, extensive intervention with multiple modalities, 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 for which services for the affected individual and their family are entitled. Many useful services include early identification and assessment, transportation, speech–language therapy, audiology, psychology and counseling services, physical and occupation therapy, medical services for diagnosis, assistive technology, adapted physical education, parent training and counseling, and preparation for an occupation following completion of school. Some of the characteristics of effective in-school interventions for language and social skill building are curriculum driven and learning theory based. These and other services can be organized into the affected child's individualized education plan. Behavioral interventions using reward contingencies are also commonly used. Funding for such programs, however, and access and availability varies from community to community. 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 disruptive and very dysfunctional children. 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. Because autism is a lifetime disability, coordination of care over a long period of time, by the physician, is essential toward efficient and rational use of resources and informed treatment planning.

12.1. Overview of Behavioral Treatments

Behavioral interventions should be one of the first interventions applied to reduce excess and disruptive behaviors and to promote skills that support normal development. Language and social functioning acquisition is one target of behavioral interventions, but behavioral approaches for other aspects of functioning that have a chance to increase quality of life could be included, such as teaching toileting and other self-care skills. Another focus of behavioral intervention, instead of building skills, 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. Behavioral techniques may be applied in these areas as well.

Direct care by the physician can involve medical interventions such as medications for comorbid mental health problems, medical problems such as seizures and constipation, or could be in conjunction with a behavioral plan for behavior management. Activity level, sleep disorders, nutritional supplementation, aggression, self injury, perseverative behaviors, teeth grinding, constipation, diarrhea, and seizures may have effective treatments that can be offered for improving the quality of life and functioning of the affected child and their family.

12.1.1. Interventions for Language Deficits

Behavioral strategies to increase communication include teaching sign language or using picture representations. Each has been studied and there is some evidence that they may facilitate the acquisition of verbal language (145, 146). Applied Behavioral Analysis has a long history of work in this area. Although controversial because of the enormous time and resources required and because studies analyzing its efficacy had significant limitations that curtail the generalizability of the results, it continues to be sought out by parents (147, 148).

12.1.2. Social Skill Acquisition

Multiple approaches to tackle this fundamental hallmark of the autistic disorder have been proposed. The clinician might recommend interventions such as Social Stories and Priming and Pivotal Response Training. 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 (149). Priming considers a situation or event that would usually result in challenging behavior by the patient with autism. Immediately before 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 reproduction (150, 151). 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 need for supervision by a trained staff, there is some evidence that the language and social behaviors acquired generalize to other settings (152).

12.2. Psychopharmacology

Various psychotropic medications are used to treat problems associated with autism. These medications generally are not helpful for the core symptoms, but can be effective for associated symptoms including but not limited to aggression, self-injurious behaviors, hyperactivity, impulsivity, stereotypies and repetitive behaviors, and sleep problems. Currently, there is no medication approved by the FDA to treat the core symptoms of autism. For successful management of symptoms, it is key to provide 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 education regarding the illness and support for the parents. Various surveys show that psychotropic medications are commonly used as part of a treatment program. The frequency with which they are used ranges from 45 to 55%, with antidepressants, antipsychotics, stimulants, and antiepileptic medications the most commonly prescribed medications (153–155).

12.2.1. Stimulants

Stimulants are prescribed in autism to manage hyperactivity, impulsivity, and attention span problems. Studies have shown that response rates with stimulants for these symptoms is lower in autism as compared with 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 children rated as unchanged, and 5 children exhibiting increased hyperactivity, stereotypes, dysphoria and rated as minimally or much worsened. 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 (156). In a placebo-controlled, double-blind, crossover study, 8 of 13 children with autism showed at least a 50% reduction of symptoms in response to methylphenidate on the Conners' Hyperactivity Index (157). 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 children aged 5 to 14 years with methylphenidate. Interestingly, improvement was noted, but the effect size was lower than that seen in ADHD children. In addition, only half of the group was much improved or very much improved. Approximately one in five children could not tolerate the medication (158). There are some administrative obstacles for the use of stimulants because a diagnosis of ADHD and Pervasive Developmental Disorder is not supported by DSM-IV and, therefore, certain payors may not approve insurance reimbursement for the medicine. ADHD symptoms in individuals with autism may respond to stimulant medications, although dosing needs to be individualized more carefully than for children with only ADHD.

12.2.2. Selective Serotonin Reuptake Inhibitors

The class of selective serotonin reuptake inhibitors (SSRIs) is one of the most commonly used in this population. Serotonin reuptake inhibitors are often considered to treat stereotypies and repetitive behaviors that interfere with day-to-day functioning. Autistic children are often very sensitive to environmental change and seem overwhelmed at times by sensory stimuli, so that they seem to have high rates of anxiety-like problems. SSRIs can be helpful for comorbid anxiety as well as depression. In cases in which an inventory of anxiety symptoms is taken, patients fail to fulfill full criteria, but diagnoses such as Anxiety Disorder Not Otherwise Specified and Depression Not Otherwise Specified can and should be made. In a placebo-controlled, crossover trial of fluoxetine in 45 developmentally delayed children and adolescents, fluoxetine was superior to placebo in reducing repetitive behaviors assessed by the Children's Yale Brown Obsessive Compulsive Scale (CY-BOCS) (159). In a 12-week, double-blind, placebo-controlled study, fluvoxamine was superior to placebo in 30 adults with autistic disorder. The response rate was 53% for fluvoxamine targeted repetitive thoughts and behaviors, and repetitive language use, as compared with no improvement with placebo (160). In another double-blind study involving clomipramine (a tricyclic antidepressant with significant 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 (161). Several less rigorously designed studies showed similar positive responses to fluoxetine, sertraline, fluvoxamine, citalopram, and escitalopram (162–169). The profile of side effects in these studies were somewhat atypical, as compared with groups in which autism was not part of the diagnostic picture, and included agitation, insomnia, aggression, and hyperactivity.

12.2.3. Tricyclic Antidepressants

Although the main feature of autism is deficits of high-level neurocognitive competencies, i.e., language and social interactive skills, one of the simpler to assess symptoms is stereotypies. These movements can call attention to the child's disabilities and raise the question of an autism diagnosis. Stereotypies 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 the chronic damage to joints caused by the behavior and interference in educational programming because of time spent in stereotypic behaviors. Clomipramine, a tricyclic antidepressant with significant serotonergic activity, has been used to treat stereotypies by two research groups, with significant reduction in the target behavior (170, 171).

12.2.4. Typical Antipsychotics

Before the era of atypical antipsychotics, traditional antipsychotics were widely used to address behavioral issues associated with autism. Among traditional antipsychotics, haloperidol is the most studied in this drug category. In various double-blind and controlled studies, haloperidol was effective in decreasing behavioral symptoms, irritability, and hyperactivity (172–174). As is true of the potential long-term serious side effects of these medications, including tardive dyskinesia and the expectation that these medications will need to be used chronically, careful monitoring is warranted. Surveillance for both withdrawal dyskinesias and tardive dyskinesia is obligatory in this population (175, 176).

12.2.5. Atypical Antipsychotics

Atypical antipsychotics use is widespread in pervasive developmental disorders. There are studies showing reduction in aggression, self-injurious behaviors, impulsivity, hyperactivity, and repetitive behaviors. Because sleep difficulties are common in this population, some atypical antipsychotics have the added advantage of helping with insomnia. Side effects are not different in this population compared to controls, with metabolic syndrome a very serious obstacle to continued use of these medications. Patients should be carefully monitored for weight gain and metabolic abnormalities.

Risperidone is the most studied atypical antipsychotic in this population. There are numerous short- and long-term controlled and open-label studies showing efficacy of risperidone in autistic children and adolescents (177–182). The landmark multisite, randomized, double-blind study conducted by the RUPP Autism Network demonstrated a positive response to risperidone. 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) for 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 with 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 were responders, versus 12% (6 of 52 children) 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 with placebo at 0.8 kg. Other side effects that were more common in the risperidone group include increased appetite, fatigue, drowsiness, dizziness, and drooling (182). Risperdal has now been approved for the treatment of autism by the FDA and may be especially useful for the disruptive and aggressive behavior sometimes associated with this disorder.

Unfortunately, currently there are no controlled studies of atypical antipsychotic use in autistic disorder, other than risperidone. In two open-label studies with olanzapine, positive response was documented on the CGI scale. The mean dose of olanzapine was approximately 8 mg/day. Major side effects were weight gain and sedation (183,184). The response to Quetiapine in two open-label studies was not as promising. In one 16-week, open-label trial involving six 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 (185). In another 12-week, open-label study involving nine youth with autistic disorder, only two of nine children at the end of the study were considered responders to quetiapine on the CGI-I scale (186). 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 the CGI scale. Transient sedation was the most common side effect. No cardiovascular side effects were noted. Five patients lost weight, five had no weight change, and one gained weight at the study endpoint (187). Preliminary results with aripiprazole were promising in a case series involving five youth with pervasive developmental disorders and maladaptive behaviors. No significant adverse effects were reported (188).

12.2.6. Anticonvulsants

Autism is approximately 70% comorbid with seizures. Good seizure control is essential in these children and adolescents because complications of the seizures confer increased morbidity and mortality. Thus, it is not uncommon for various antiepileptic medications to be used in this population. Some of the anticonvulsants, such as divalproex sodium and carbamazepine, have an added advantage of helping with mood lability and behavioral issues. However, there is very limited

data looking at the effectiveness of these agents in autism. In a recent 13-week double-blind, placebo-controlled study involving 13 individuals with autism spectrum disorder, divalproex sodium was superior to placebo in reducing repetitive behaviors as measured by CY-BOCS (189). In a retrospective study of divalproex sodium in 14 individuals with pervasive developmental disorders, 10 patients (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 (190).

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 (191). In a double-blind, placebo-controlled study involving 27 youth with autistic disorder, lamotrigine was not found to be effective as compared with placebo (192). The use of antiepileptics as mood stabilizers may play a role in cases where comorbid bipolar disorder can be diagnosed.

12.2.7. 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 (193). In another controlled, double-blind study involving eight boys with autistic disorder; clonidine was modestly effective in reducing irritability and hyperactivity (194). 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 (195). An open trial of a beta-blocker reported benefit in reducing aggression in autistic disorder (196).

12.2.8. Naltrexone

Because opiate receptors have been implicated in the psychopathology of autism, naltrexone, an opiate antagonist, had been suggested for treatment of autistic disorder. Research studies have shown mixed responses. 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 (197–200). Double-blind, placebo-controlled studies of naltrexone in autism failed to show any positive effects on communication, social interactions, stereotypies, and self-injurious behaviors (201–203).

12.3. Unproven Treatments

There are advocates for a panoply of ineffective treatments. The application of these sometimes harmful interventions need to be addressed head-on with the zealots who push for their implementation. A frank discussion regarding their merits with caregivers is required. Studies of secretin, a gut enzyme (204), B6 and magnesium (205), and antifungal treatments (128) 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, oxytocin infusion, omega-3 fatty acids, and carnitine (206). 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 interventions that alleviate symptoms and the family's burden for the care of children with autism 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 national research agenda with products made rapidly available to physicians for their patients.

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21
Childhood Anxiety Disorders

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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. Several pathways of etiology are presented, specifically genetics, parent–child attachment, parental anxiety and parenting style, and life experiences. Six of the common childhood anxiety disorders, separation anxiety disorder, specific phobia, social phobia, 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 · Generalized anxiety disorder · Obsessive–compulsive disorder · Panic disorder · Separation anxiety disorder · Social phobia · Specific phobia

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 regarding childhood anxiety disorders are rapidly increasing. Childhood anxiety disorders is currently a topic of high interest to researchers and practitioners.

Anxiety disorders are separated into two sections of the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition, text revision (DSM-IV-TR) manual (2). The anxiety disorder section contains criteria for the following disorders: 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. These diagnoses can be applied to children, adolescents, and adults. In addition, there is a section for disorders usually first diagnosed in infancy, childhood, or adolescence, which includes the criteria for separation anxiety disorder (SAD). This chapter begins with an overview of the epidemiology and etiology of childhood anxiety disorders, reviews six of the common childhood anxiety disorders, and then summarizes effective treatment approaches.

1. Epidemiology

Several issues make childhood anxiety disorders one of the most difficult areas to study in a representative sample (1). First, several of the disorders (e.g., OCD, 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 because of their lack of psychological awareness of symptoms associated with anxiety. Although there are obstacles in determining the prevalence of childhood anxiety disorders, considerable progress has been made during the past decade.

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% (3, 4); 6-month estimates range from 5.5 to 17.7% (5,6); 12-month estimates range from 9.3 to 20.9% (7, 8); and lifetime estimates range from 8.3 to 27.0% (9). These epidemiologic studies are composed of samples of children and adolescents who are primarily white. There is little known regarding the manifestation and presentation of childhood anxiety disorders across racial and ethnic groups.

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 (aged 24 to 71 months)

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(10). 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 were found across anxiety disorders, with 6.5% of children diagnosed with GAD, 2.4% with SAD, 2.3% with specific phobia, 2.2% with social phobia, and 0.6% with selective mutism. 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%) (10).

Costello and colleagues (3) 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 phobia, 0.3% with specific phobia, 0.17% with OCD, and 0.03% with panic disorder. Costello and colleagues (11) 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 phobia, 0.2% with specific phobia, and 0.2% with panic disorder. In addition, the overall prevalence of anxiety disorders was greatest in children 9 to 10 years of age (4.6%) and was the lowest at 12 years of age (0.9%). The diagnoses then increased in prevalence after 12 years of age. Specifically, the transition to adolescence resulted in an increase in social phobia in girls only and an increase in panic disorder and GAD across sexes.

Females are more likely to endorse an anxiety disorder compared with males; however, when sex differences are examined in each diagnosis, these differences tend to be small (1). Lewinsohn and colleagues (9) conducted the Oregon Adolescent Depression Project to examine prevalence rates in more than 1,700 adolescents. Results showed that 2.8% of the adolescents endorsed at least one current anxiety disorder. Sex 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 girls compared with boys. This sex difference was present by 6 years of age, as determined by retrospective reports, at which time, twice as many girls compared with boys had already experienced an anxiety disorder. The mean age of onset did not significantly differ between boys (mean, 8.5 years; standard deviation [SD], 3.8 years) and girls (mean, 8.0 years; SD, 3.9 years); however, girls were given new diagnoses of anxiety disorders at a faster rate than boys.

2. Etiology

2.1. Genetics

Genetic factors seem to play a role in the etiology of childhood anxiety disorders. Goldsmith (12) reviewed epigenetic approaches to understanding developmental psychopathology, and found heritability estimates of 40 to 58% for internalizing symptoms using the Child Behavior Checklist with community samples from several studies. Furthermore, a heritability estimate of 59% was found for anxiety symptoms using the Revised Children's Manifest Anxiety Scale (13). Effects of the shared environment on anxiety symptoms range from noncontributory (13) to significant (14). In summary, previous studies indicate moderate heritability of internalizing symptoms in children.

Behavioral inhibition is a genetically based, temperamental trait that is characterized by a child's tendency to react to novel or unfamiliar situations with restraint, distress, or avoidance (15). This trait can be measured in the laboratory setting beginning at 9 months of age (15). In prospective studies of toddlers with and without behavioral inhibition, findings at 3-year follow-up demonstrated that behavioral inhibition was associated with an increased risk of avoidant disorder (DSM-III-R diagnosis for children with social phobia), SAD, and agoraphobia (16). Biederman and colleagues (17) emphasized that the risk for developing anxiety disorders is greater in children with a history of persistent shyness and inhibition from 21 months to 7.5 years of age, and that the risk increases further if the parents have a history of an anxiety disorder. Subsequently, a specific link between behavioral inhibition in toddlers and social phobia in adolescents was delineated, with approximately one third of inhibited toddlers manifesting symptoms of social phobia as teenagers (18).

A large community sample of Australian children (2,443 children) was studied from infancy to adolescence to assess whether shy–inhibited temperament is predictive of later anxiety disorders (19). Every 18 months, participants were assessed with parent, teacher, and self-report rating scales. Logistic regression analyses demonstrated that shy temperament was associated with increased likelihood of anxiety symptoms, especially at ages 9 to 10 years and 12 to 13 years.

2.2. Attachment

Another factor that seems 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 (20). In a study beginning in the third trimester of pregnancy, mothers and their children were studied prospectively (21). 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. In the regression analyses, this result explained a greater percentage of the variance than the child's temperament or maternal history of anxiety in predicting the later presence of anxiety diagnoses.

2.3. Parental Anxiety and Parenting Style

Children of parents with anxiety disorders are at increased risk of developing anxiety disorders (e.g., 22,23). Merikangas and colleagues (24) examined psychopathology among youth (aged 7 to 18 years) of parents with substance abuse or anxiety disorders. Results indicated that children of parents with anxiety disorders were two times more likely to have anxiety disorders compared with children of substance abusers or control subjects. Studies consistently demonstrate that children of mothers with anxiety disorders are at greater risk of being diagnosed with anxiety disorders compared with children of mothers without anxiety disorders (e.g., 25,26). Beidel and Turner (27) demonstrated that children were nearly five times more likely to be diagnosed with an anxiety disorder when parents met criteria for an anxiety diagnosis.

Donovan and Spence (28) hypothesize that parental anxiety is a risk factor that is not independently causal but is mediated or moderated through a different mechanism (e.g., parenting style). There are two main factors in parenting style that have emerged as most relevant to the development of childhood anxiety disorders: parental warmth/rejection (positive versus negative feelings the parent has toward the child) and parental control (degree to which parental behaviors are designed to protect the child from possible harm) (29). Hudson and Rapee (30) conducted an observational study in which children completed two difficult cognitive tasks while their mothers were asked to sit nearby and provide support. The results showed that mothers of anxious children were more involved, more intrusive, and more negative compared with mothers of control children. Furthermore, parents of anxious children are significantly more likely to agree with and encourage their child's avoidance when discussing ambiguous hypothetical situations compared with parents of control children or aggressive children (31). This may suggest to the child that the world is a dangerous place, which may interfere with the child's ability and desire to learn otherwise (29).

2.4. Life Experiences

The development of anxiety in children may be related to exposure to negative life events (32). Muris and colleagues (33) studied the development of worries and fears in healthy children, and found that 54% of children attributed the origin of their primary worry to a conditioning experience (e.g., death of grandparent), 33% reported an information pathway (e.g., news reports on television), and 13% reported a modeling experience (e.g., seeing parents worried). Another study by Muris and colleagues (34) reported that threatening or aversive life events were not critical in the development of worry in children diagnosed with overanxious disorder/GAD. Results indicated that only 7.7% of children with overanxious disorder/GAD related their worry to a negative conditioning experience.

An integrated model for the development of childhood anxiety disorders has been presented by Manassis and Bradley (20). In this model, temperament, attachment, social systems, and the interplay among them are incorporated as important factors that contribute to the development of childhood anxiety disorders. One single component does not seem to offer a complete explanation of the development of anxiety disorders in children and adolescents.

3. Separation Anxiety Disorder

Separation anxiety is a normal developmental process that results in appropriate distress after separation from attachment figures (35). Separation anxiety typically occurs in children from 6 to 30 months of age and generally intensifies when the child is 13 to 18 months old. The frequency and intensity of separation anxiety normally decreases between ages 3 to 5 years because of 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 (35).

3.1. DSM-IV-TR Criteria

Separation anxiety is considered clinically significant when it exceeds developmental norms and is associated with impaired functioning. According to the DSM-IV-TR (2), the essential feature of SAD is excessive and persistent anxiety about being away from home or an attachment figure (i.e., parents, grandparents, other primary caregivers, or siblings). Common characteristics of children 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. To be diagnosed with SAD, the anxiety must persist for at least 4 weeks, be present before 18 years of age, and cause significant distress or impairment in social, academic, or other areas of functioning.

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 (3, 36, 37). Some studies suggest that SAD is more common in females (38); whereas, other

studies suggest that there are no significant sex differences (3, 39).

Symptom presentation in SAD seems to manifest differently across the age span, with younger children exhibiting more symptoms compared with older children (40). Children aged 5 to 8 years old most commonly report anxiety regarding harm to attachment figures and school refusal. As children reach 9 to 12 years of age, symptoms typically manifest as significant distress during times of separation. During adolescence, school refusal and somatic complaints are most common.

In a study of 199 children (ranging from 8 to 13 years) diagnosed with SAD, GAD, and/or social phobia, children with SAD had the greatest mean number of comorbid diagnoses (41). The most frequent comorbid diagnoses with SAD included GAD in 74% of children, specific phobia in 58%, attention-deficit hyperactivity disorder (ADHD) in 22%, social phobia in 20%, and oppositional defiant disorder in 12%. The likelihood of comorbid mood disorders was significantly lower in children with a primary diagnosis of SAD (2%) compared with children with a primary diagnosis of GAD (17%) or social phobia (15%).

3.3. Course and Outcome

The mean age of onset of SAD typically falls between 7 and 9 years (39). Kearney and colleagues (35) 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 toward 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 (mean, 10.9 years) (42). 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 oppositional defiant disorder, 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 and a new diagnosis of depressive disorder.

Studies have indicated that childhood SAD may be a risk factor for other anxiety disorders in adulthood (43). There is conflicting evidence regarding whether SAD may be specifically related to later development of panic disorder. Approximately 50 to 75% of children and adolescents with juvenile panic disorder have a previous or comorbid diagnosis of SAD (44, 45). Research has suggested that a history of childhood SAD may be related to a specific heritable early onset form of panic disorder (46), whereas other researchers hypothesize that childhood SAD does not change into another anxiety disorder, but rather persists into adulthood with a different symptom presentation that is more relevant to adult issues (e.g., avoidance of being alone) (47, 48). One study completed a 7-year follow-up with youth who had participated in treatment for an anxiety disorder during childhood (49). The results indicated that 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 phobia. It is important to note that a diagnosis of SAD was not more predictive of a later diagnosis of panic disorder. Overall, these studies suggest that SAD is likely linked to adult anxiety disorders, but not specifically to panic disorder.

4. Fears and Specific Phobias

The majority of children and adolescents experience fears throughout development (50). 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 they are mediated by children's daily experiences and cognitive capacities (51). 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.

4.1. DSM-IV-TR 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 other (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.

4.2. Clinical Presentation

There seem to be differences in the prevalence rates of specific phobia found in children from community versus clinical samples. The prevalence of specific phobia in studies using

community samples of children and adolescents ranges from 2.6 to 9.1%, with an average of approximately 5% across studies (50). The prevalence of specific phobia in clinical samples of children and adolescents is estimated to be approximately 15% (52); however, this may be an overestimate of actual occurrence because of a failure to document impairment caused by symptoms.

In a study examining the specific phobia symptoms in nearly 1,000 children and adolescents ranging in age from 7 to 19 years, girls endorsed more specific phobia symptoms compared with boys (53). In addition, children younger than 13 years of age endorsed a greater frequency of specific phobia symptoms compared with older children. Participants often simultaneously endorsed different types of specific phobias, which suggests that phobias frequently co-occur. Sex differences were confirmed in a later study that examined phobias in twins who ranged in age from 8 to 9 years of age (54). Not only were specific phobias more common in girls, but girls also exhibited significantly higher levels of fear intensity compared with boys.

Each specific phobia subtype seems to have a unique manifestation of physical and cognitive symptoms (55, 56). The individual's response to exposure to the feared stimulus differs based on the type of phobia. Exposure in cases of an animal phobia results in sympathetic activation (i.e., tachycardia), which elicits heightened arousal; whereas exposure in cases of a 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 specific phobia compared with other anxiety disorders in community samples of children and adolescents (57). In contrast, studies using clinical samples of children and adolescents with a primary diagnosis of specific phobia showed that 64 to 72% of the participants presented with at least one additional psychiatric diagnosis (52, 58).

4.3. Course and Outcome

Childhood phobias may develop after a frightening experience, after observing a terrifying reaction in others, or when learning about fears (59, 60). 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 to 40% of children diagnosed with phobias continue to demonstrate phobias at a later point in time (61). Avoidance behavior is likely responsible for the maintenance of 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 (62).

5. Social Phobia

Before 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 are now most commonly diagnosed with social phobia.

5.1. DSM-IV-TR Criteria

Social phobia is characterized by marked and persistent anxiety regarding social or performance situations that is caused by fears that the individual will act in a way that is embarrassing or humiliating (2). For example, children with social phobia 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 several exceptions in the DSM-IV-TR criteria for social phobia in children compared with adults. Children with social phobia must demonstrate the capacity for normal peer relationships; anxiety must occur in settings with peers as well as with adults; anxiety symptoms may take the form of crying, tantrums, freezing, or avoidance of social situations; and children may not realize their fears are extreme or unreasonable. Social phobia symptoms must cause interference in the daily 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 phobia have the generalized type (63, 64) that is characterized by fear of most social or performance situations.

5.2. Clinical Presentation

The mean age of onset of childhood social phobia in a clinical setting is reported to range from 11.3 years (39) to 12.3 years (65). Social phobia is diagnosed more frequently in girls compared with boys (66). However, there are no sex differences in the presentation of social phobia (63, 67). Studies have been conducted to examine the clinical presentation of children and adolescents diagnosed with social phobia. Beidel and colleagues (63) evaluated a clinic sample of 50 children with social phobia (aged 7 to 13 years). Results indicated that children with social phobia manifested poor social skills and used maladaptive coping behaviors (e.g., avoidance) in social or performance situations. Children with social phobia 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.

In a nonclinical sample of 7 to 11 year olds, children with social phobia (n = 45) were compared with anxious children without social phobia (n = 56) to identify characteristics unique to social phobia (64). Children with social phobia feared and avoided a significantly greater number of social situations than anxious children without social phobia. In addition, significantly more children with social phobia compared with anxious children without social phobia described difficulty making friends (49% versus 24%, respectively) and significantly more preferred to be alone rather than with peers (24% versus 7%, respectively). According to teacher report, children with greater severity of social phobia symptoms exhibited significantly poorer social skills, poorer leadership skills, increased attention difficulties, and greater learning problems.

Children with social phobia have negative cognitions in social situations, viewing themselves as less socially adept than their peers (68). They expect poor outcomes in social settings, and, in fact, fare less well in social interactions. Social phobic children report negative peer interactions (67). Children with social phobia compared with children who are not anxious are more likely to be ignored, excluded, and rejected by classmates (68).

Children and adolescents with social phobia frequently have a comorbid disorder. Beidel and colleagues (63) found that 60% of children (7 to 13 years old) with social phobia met criteria for another diagnosis. Thirty-six percent had another anxiety disorder, 10% had ADHD, 8% had selective mutism, and 6% had an affective disorder.

5.3. Course and Outcome

Social phobia often begins during preadolescence and typically has a chronic course throughout adulthood (69, 70). A diagnosis of social phobia may be associated with social, educational, and occupational impairments. Common negative outcomes of social phobia in adults include social isolation, difficulty holding jobs, depression, drug abuse, and suicide attempts (69, 71–74). Because of avoidance of performance and social situations and other impairments related to social phobia, many individuals fail to graduate from high school (75). 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%) (76). In addition, 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 because of social phobia symptoms.

6. Generalized Anxiety Disorder

Before 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 overanxious disorder. Overanxious disorder 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.

6.1. DSM-IV-TR Criteria

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 associated 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 physical symptoms cause significant impairment or distress in important areas of functioning.

6.2. Clinical Presentation

Because the diagnosis of GAD is relatively new in children and adolescents, there is limited information regarding epidemiology and some of the available data refer to children and adolescents with overanxious disorder. Prevalence estimates of GAD in a general population (15 to 54 years old) are approximately 1.6% current and 5.1% lifetime, with approximately twice the occurrence in female individuals compared with male individuals (77). Pina and colleagues (78) examined which worry domain was most predictive of a diagnosis of GAD in a clinic sample of 111 children and adolescents (6 to 17 years old). Results showed that uncontrollable excessive anxiety regarding 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).

Masi and colleagues (79, 80) examined the symptom presentation in clinical samples of children and adolescents diagnosed with GAD. Masi and colleagues (79) interviewed 58 subjects ranging in age from 7 to 18 years 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%). Children and adolescents with GAD also endorsed other symptoms at a lower rate, including psychomotor agitation (31%), difficulty sleeping (34%), and fear of being alone (36%). Significant differences in symptom presentation were not found between sexes (79,80). One study (79) found differences across age groups when comparing children (7 to 11 years) and adolescents (12 to 18 years), with children reporting a higher need for reassurance and adolescents reporting more frequent brooding. A subsequent study

did not find differences in GAD symptom presentation across age groups (80).

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 (81). 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 (81). Both children and adolescents seem to worry frequently about social acceptability, personal competence, and expectations about the future (79).

Other anxiety disorders and mood disorders are frequently comorbid with a diagnosis of GAD in children and adolescents. A study of 157 children and adolescents with GAD showed that 93% of participants endorsed a comorbid disorder (80). 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 because of the symptoms that are common across disorders, such as impaired concentration and sleep difficulties (82). In addition to comorbid internalizing disorders, 21% of the participants met criteria for a comorbid externalizing disorder (ADHD, oppositional defiant disorder, conduct disorder) (80).

Because 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 (45). Specifically, participants with GAD and a comorbid depressive disorder endorsed a greater number of anxiety symptoms and greater irritability.

6.3. Course and Outcome

Age of onset of GAD seems to have a bimodal distribution with an early onset occurring during childhood and adolescence and a later onset occurring during adulthood (77). The prevalence rate of GAD tends to increase with age from childhood to adulthood (79). Childhood-onset GAD is often associated with a greater degree of psychopathology compared with adult-onset GAD (83). Early diagnosis of GAD is important because a misdiagnosis or lack of treatment significantly increases the likelihood of a chronic course and a low remission rate throughout adulthood (84). 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 (79). In addition, children with GAD were more likely to begin drinking alcohol at an earlier age compared with other children (85).

7. 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 (86). 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.

7.1. DSM-IV-TR Criteria

In the DSM-IV-TR (2), either obsessions or compulsions with the associated characteristics are needed to qualify for a diagnosis of OCD. Obsessions are recurrent, persistent ideas that 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 hour per day engaged in obsessions and/or compulsions, or experience functional impairment because of OCD. In adults, the individual must recognize that the obsessions or compulsions are irrational or excessive; this criterion is not required in children because children often have poor insight into their symptoms.

7.2. Clinical Presentation

The prevalence of OCD has been examined more thoroughly in adolescents compared with children. Heyman and colleagues (87) 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 to 7 years, 0.026%; 8 to 10 years, 0.14%; 11 to 12 years, 0.21%; and 13 to 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 (88–90). In children, the male to female ratio is approximately 3:2 (91), with the sex ratio approximately equal in adolescents (92).

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 (93). 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 caused by OCD (93). 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 because of the frequency and complexity of the rituals (e.g., children who are late to school because of repeated hand washing and checking behaviors before leaving the house).

OCD characterized by both obsessions and compulsions is the most common presentation in youth (94, 95), and it is rare that children experience obsessions without compulsions (94). 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 (94). The most frequent compulsions included excessive washing (e.g., hand washing, showering, tooth brushing) in 85% of children and adolescents, repeating rituals in 51%, and checking in 46%. In a consecutive series of 94 children and adolescents with OCD, aggressive sexual obsessions, symmetry obsessions, checking, and repeating rituals were associated with comorbid tic disorders (96).

A subgroup of children with OCD and/or tic disorders has been characterized as having pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (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 (documented with positive streptococcal throat culture and/or elevated antistreptococcal titers) and symptom onset and exacerbation; 5) neurological symptoms (e.g., hyperactivity, choreiform movements) (97). 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 (98).

Comorbidity is frequently documented in children and adolescents with OCD. Zohar (99) completed a review of children and adolescents with OCD, and estimated that approximately 66% had a least one other diagnosis. Heyman and colleagues (87) found 76% of the children and adolescents with OCD had at least one comorbid diagnosis. Tic disorders are commonly associated with OCD in children, with a comorbidity rate of approximately 21% (92).

7.3. 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 (mean, 10.3 years) (92), whereas the mean age of onset in adults is 21 years (100). 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 (92, 101). Many children experience a single obsession or compulsion at the time of onset, which then gradually shifts 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 (mean, 5.7 years) demonstrated that rates of persistence of OCD were lower than previously thought (102). 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.

8. Panic Disorder

There is limited research on panic disorder in children and adolescents because there was previous speculation that panic disorder only occurred in adulthood (103). The first report of panic symptoms in adolescents was published in 1984 (104), and, since that time, studies have been conducted that indicate that symptom presentation is similar across ages and that panic disorder can be diagnosed in children and adolescents.

8.1. DSM-IV-TR Criteria

The DSM-IV-TR (2) defines a panic attack as a discrete period of intense fear and discomfort in which physical or cognitive symptoms (e.g., accelerated heart rate, sweating, shaking, shortness of breath, fear of losing control) develop abruptly and peak within 10 minutes. To meet diagnostic criteria for panic disorder, the attacks must be uncued and occur without an identifiable precipitating factor. In addition to having these recurrent, unexpected, and uncued panic attacks, the individual has persistent concern about experiencing another attack, worries about the consequences of a future attack, or makes significant changes in behavior because of fear of having another attack. Individuals diagnosed with panic disorder are categorized into two groups, with or without agoraphobia. Agoraphobia exists when the individual experiences anxiety regarding being in situations in which help is not available or escape is difficult in the event that a panic attack occurs, which results in avoidance of certain situations (i.e., crowded places, traveling alone).

8.2. Clinical Presentation

Panic attacks are found to occur in children and adolescents at a significantly higher rate than panic disorder. Essau and colleagues (103) interviewed 1,035 adolescents (12 to17 years old) from a nonclinical sample, and found a lifetime prevalence rate of 0.5% for panic disorder and an 18% prevalence rate for at least one panic attack. Masi and colleagues (105)

found a higher prevalence of panic disorder, at 10.4%, in a clinical sample of 220 children and adolescents (7 to 18 years old).

Masi and colleagues (105) examined the presentation of panic attacks in children and adolescents diagnosed with panic disorder. Participants reported high frequencies of the following symptoms: palpitations (87%), sweating (74%), sensation of shortness of breath (61%), feeling of dizziness (52%), and trembling (52%). The symptoms that were endorsed at the lowest frequency included paresthesias (26%), fear of losing control or going crazy (22%), and sensation of choking (19%).

Studies have examined the description of panic attacks in children and adolescents, and have found consistent differences across the developmental lifespan (44, 106, 107). 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. The occurrence of cognitive symptoms associated with panic attacks seems to be related to age and tends to occur after the development of physical symptoms (44). 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) (44).

High rates of comorbidity have been documented in children and adolescents diagnosed with panic disorder. Masi and colleagues (105) 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.

8.3. Course and Outcome

Researchers have expressed doubt regarding whether panic disorder occurs in young children because of their inability to experience the cognitive symptoms associated with the disorder (105). 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 relative importance of age and pubertal stage in 754 sixth- and seventh-grade girls to improve understanding of panic attacks during adolescence (108). The participants completed a structured clinical interview regarding the history of panic episodes and a self-assessment of Tanner stage of pubertal development. Results indicated that 5.3% of the girls 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.

The mean age of onset of panic disorder is typically during early to middle adulthood (109). 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 (110–112). Children and adolescents who experience panic attacks may have a chronic course throughout adulthood, and there is a substantial potential for further psychopathology (i.e., major depression, bipolar disorder, anxiety disorders) after panic attacks (44, 113, 114). However, some individuals experience panic attacks and do not develop psychopathology (115). A prospective study with 2,246 high school students examined factors that contribute to differential trajectories after initial panic attacks (116). Results found that anxiety sensitivity, negative affect, and childhood behavioral inhibition significantly predicted the severity of panic attacks and the development of internalizing symptoms after 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 (117). It has been shown that early onset panic disorder (before 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 (118).

9. 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 (119). In addition, the following medications may be associated with anxiety symptoms as side effects: antiasthmatics, sympathomimetics, steroids, selective serotonin reuptake inhibitors (SSRIs), antipsychotics, atypical antipsychotics, and stimulants (119). 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. After a complete assessment, a multimodal treatment

approach should consider psychosocial and psychopharmacology components (119).

9.1. Cognitive–Behavioral Therapy

Although numerous psychosocial approaches are 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 (120). Velting et al. (121) 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. During the past decade, numerous CBT 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 (122, 123).

Kendall (122) conducted the first randomized controlled study to assess the outcome of a manual-based CBT intervention referred to as the *Coping Cat* (124). Forty-seven participants, aged 9 to 13 years old, with primary diagnoses of overanxious disorder, SAD, or avoidant disorder (social phobia) 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 after the waiting period. Follow-up assessments at 3 years (125) and 7.5 years (126) 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 (123) used the *Coping Cat* intervention program to examine these group differences in 37 children aged 8 to 14 years old with a primary diagnosis of GAD, SAD, or social phobia. Results indicated that the individual CBT and group CBT were equally effective and both were more effective than the wait-list control. After 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 waiting list no longer met criteria after the waiting period. Flannery-Schroeder and colleagues (127) 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.

A series of studies has demonstrated the efficacy of family CBT conducted in a group format (128–130). Silverman and colleagues (128) completed a randomized clinical study with 56 children 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 (129) 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 (aged 6 to 10 years) who had a primary diagnosis of SAD, GAD, or social phobia (130). The results indicated that 69% of children who completed *FRIENDS* no longer had a diagnosis, compared with 6% of children on the waiting list.

Studies have also been completed to evaluate the role of parental involvement in the treatment of childhood anxiety disorders (131, 132). Barrett and colleagues (131) compared anxious children who participated in a CBT intervention that included a family therapy component 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 after treatment and at 1-year after treatment; however, these differences were not present at 6 years after treatment (133). 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 (132). Cobham and colleagues (134) 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 (135, 136). Dadds and colleagues (135) screened 1,786 children from Australia in the third through sixth grades and identified 128 children 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 after treatment, 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 (136) expanded on the research conducted by Dadds et al. by implementing the *FRIENDS* program in elementary schools in the United States. Sixty-one children (aged 7 to 11 years) across three elementary schools were identified as anxious and randomized by school to group CBT for children, group CBT for children plus a concurrent

parent training group, or a no-treatment control group. Findings showed that children who participated in either CBT treatment condition had a significant decrease in anxiety and associated impairment after treatment 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.

9.2. 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 because of the symptoms. 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. Several randomized, double-blind, placebo-controlled studies demonstrate the efficacy of SSRIs in decreasing anxiety symptoms and support their short-term safety in children and adolescents with anxiety disorders (137–140).

9.2.1. Selective Serotonin Reuptake Inhibitors

A multicenter study examined 8 weeks of fluvoxamine versus placebo for 128 children and adolescents aged 6 to 17 years with SAD, GAD, and/or social phobia (137). Dosage of fluvoxamine was 50 to 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 after treatment. In addition, the Clinical Global Impressions (CGI) Improvement scale (141) 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 because of 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, 22 youths aged 5 to 17 years with a primary diagnosis of GAD were treated with sertraline (maximum dosage, 50 mg/day) or placebo for 9 weeks (138). 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, 74 children and adolescents (aged 7 to 17 years) with SAD, GAD, and/or social phobia were treated with 20 mg/day fluoxetine versus placebo for 12 weeks (139). Sixty-one percent of the children who received fluoxetine versus 35% who received placebo were rated after treatment 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 10 to 50 mg/day paroxetine versus placebo in 322 children and adolescents aged 8 to 17 years with social phobia (140). After treatment, 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 because of side effects was uncommon, with 6% of the children on paroxetine leaving the study because of 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.

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 (142). 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 (142).

9.2.2. Tricyclic Antidepressants

Five placebo-controlled studies of tricyclic antidepressants (TCAs) for SAD or school refusal show contrasting results (143–147). One study supports the efficacy of a TCA for SAD (143) 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 (144). 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 because of low medication dosage (145) or small sample sizes (146, 147). Together, 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 because of 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. Because of these drawbacks and the inconsistent findings regarding their efficacy, TCAs are a second-line choice for treating anxiety disorders in children. Unlike studies conducted with TCAs, recent studies using SSRIs consistently support the efficacy of SSRIs for anxiety (137–140). Thus, SSRIs are the first choice for treating anxiety in youth.

Clomipramine, a TCA with serotonergic properties, is strongly supported in the literature as efficacious in the treatment of OCD in children (148–150). A meta-analysis of 12 studies compared SSRIs (fluoxetine, fluvoxamine, paroxetine, sertraline) and clomipramine in the treatment of OCD in youth (151). Results showed that clomipramine was 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 because of the drawbacks of TCAs, as discussed above. Clomipramine is usually reserved for treatment or augmentation in severely symptomatic children or children who have failed to respond to SSRI treatments (151).

9.2.3. Black Box Warning

The US 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 developing suicidal ideation or suicidal behavior while receiving an SSRI or another antidepressant (152). In addition, the FDA recommends close monitoring of all youth on antidepressants with weekly visits to the physician in the first month of medication treatment, followed by biweekly visits in the second month, and then a follow-up at 3 months. 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 (153). 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 (153). Thus, it seems that the small risk of suicidal ideation and behavior on antidepressants occurs in youths with a diagnosis of major depression, and not in those with an anxiety disorder without major depression.

Because of the efficacy of SSRIs (137–140), the low incidence of serious suicidal events in youth on antidepressants, and the potential for serious negative outcomes in youth with untreated anxiety, there is ample support for the carefully monitored, appropriate use of SSRIs in the treatment of children and adolescents with anxiety disorders (154, 155).

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22
Schizophrenia in Children and Adolescents

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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, is discussed.

Keywords Adolescent · Antipsychotic medications · Brain imaging · Neuropsychology · Schizophrenia

1. Introduction

Increased attention has been paid to schizophrenia occurring in children and adolescents during the last 10 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, has come a focus not only on young adults but also teenagers. Thirdly, first-line atypical antipsychotic medications have been available for a little over a decade and are approved for the treatment of schizophrenia in adults, but are frequently used in adolescents with the illness. 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.

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 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. As noted earlier, 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.

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.

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Starting with the diagnosis of schizophrenia during adolescent years, it is now well accepted that teenagers can have symptoms similar to those seen in adults, and when they fulfill the criteria outlined in the *Diagnostic and Statistical Manual*, 4th edition (DSM-IV), 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 in recent years 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 that are more recent 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 was stable during at least the first 6 months of the study, and that conversion of bipolar disorder in these rigorously identified youth was uncommon (2).

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 (3).

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 (4, 5). 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 (6) 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 is currently developing, with scales emerging from some groups (7).

Therefore, recent research indicates that the diagnosis of schizophrenia can be applied to children and to adolescents using criteria from DSM-IV. The criteria are the same as those in adults and once the diagnosis has been made, they seem to be 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. (6) 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.

3. Epidemiology

It is well known from worldwide epidemiologic studies that schizophrenia is present in approximately 1% of the population (8). 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 (9). 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 (10). This figure drops to 26% for young women. Another first episode study is informative for the onset of schizophrenia, 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 (11).

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 (12), 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.

4. Pathophysiology

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% (13). In addition, the family aggregation is not changed by being raised by an adoptive family (14, 15). With the emerging technology of molecular biology, there has been a collection of genes that are statistically associated with schizophrenia. Many of these genes are known to be associated with how neurons interact (16).

Regarding schizophrenia in children and adolescents, Gornick and colleagues (17) posited that the severity of an illness increases with earlier onset. In this recent report, the research group has identified an association between the dysbindin gene and early onset schizophrenia.

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 (18) 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. (19) 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 (20) have shown decreased white matter integrity in brains of adults with schizophrenia. Recently, White and colleagues (21) have shown white matter abnormalities in the hippocampal region of the brain. (Fig. 22.1 and Color Plate 4, following p. 650) illustrates this finding.

The development of non-invasive 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) (22, 23) and magnetic resonance imaging (MRI) studies (24) to showing functional changes using positron emission tomography (PET) scanning and functional MRI (25). 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 (26) or neurotransmitters such as glutamate (27). 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 (28, 29). The authors noted the similarity to findings in adults and consistency with the neurodevelopmental model of schizophrenia. Later, MRI structural scans noted differences from control subjects in the ventricular as well as cortical areas of the brain (30, 31).

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 (32).

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 (33, 34). These dynamic changes in brain at the onset of the illness and possible differences in effects of medications—traditional versus atypical antipsychotics—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 (21).

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 (35). 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

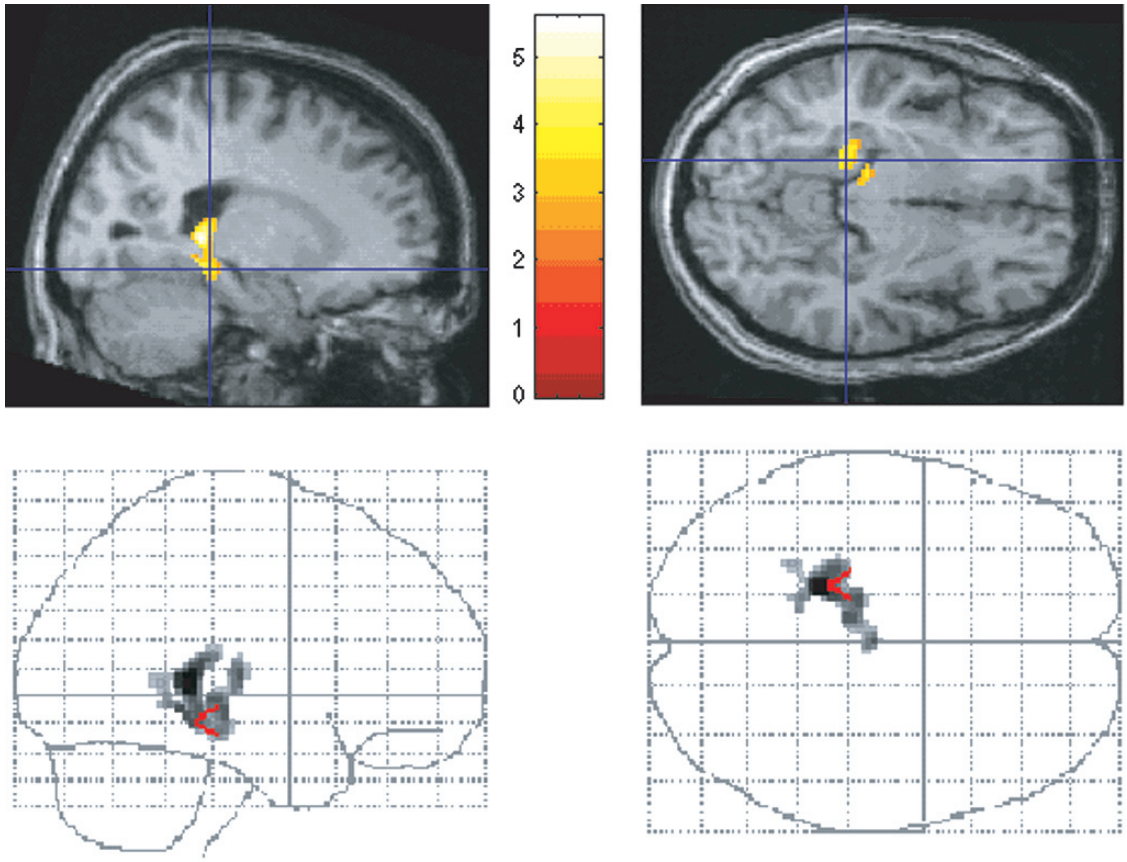

FIGURE 22.1. Reduction of fractional anisotropy (*FA*) in the posterior hippocampus in children and adolescents with schizophrenia compared with control subjects. The figures on the *top* demonstrate areas of decreased FA on the sagittal (*left*) and axial (*right*) images. The *lower* images correspond 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 (courtesy of the Youth Psychosis Research Group at the University of Minnesota; further information is described in reference (21)). (*see* Color Plate 4, following p. 650)

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 implementation of appropriate treatment.

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 complement 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 (36). 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 (6) 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 (37), and they have found a remarkable stability of neuropsychological functioning during the 1-year follow-up period. This study, which is consistent with a first-episode study conducted by Hoff and colleagues (38), 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. This is an important area for further study.

Our research group at the University of Minnesota has discussed use of neuropsychological testing in treatment planning. Reasoning that neuropsychological testing is related to social and functional outcome (39), we have explored using measures such as sustained attention and working memory to assist in treatment such as planning how day hospital

treatment benefits can be maximized and also considered how these values can assist in return to work and/or school. To date, this has seemed to be helpful and well accepted, although much further work will be needed to assess actual usefulness and acceptance by patients and families.

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.

5. Treatment of Schizophrenia in Children and Adolescents

5.1. Medication Treatment

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 (40–42). 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 (43).

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 medication studies for children and adolescents. Actually, the trials that led to approval for the second-generation antipsychotic medications did not include subjects younger than the age of 18 years. Therefore, child and adolescent psychiatrists face the daunting task of interpreting data conducted on adult subjects to apply treatments to people younger than age 18 years. In many ways, this same problem occurs in the psychosocial treatments, in which controlled trials of family psychoeducation, social skills treatment, and cognitive rehabilitation treatment are underdeveloped for this age group.

The paucity 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 DUP on social and functional outcomes (44). It is ironic that, at a time that studies are indicating that long stretches of psychosis may lead to poor outcome, there are not programs to assertively identify and treat psychotic youth.

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.

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, their use in maintenance treatment (42), and new data indicating the potential for medications to improve cognitive functioning (45, 46).

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 that an adequate dose was frequently difficult to reach (47).

In preteens, there is one controlled study (48) investigating haloperidol for children. This trial also shows an advantage for this traditional antipsychotic medication at a dose of 0.5 to 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 (49–52). 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 (53). Symptoms such as galactorrhea, 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 discussed. As of now, there is not data indicating whether these side effects occur more frequently in youth than in older patients.

Olanzapine was the second of the atypical antipsychotic medications to be approved, and a case series by Findling and colleagues (54) 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. (55). 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. It is very appropriate for the field to be aware of this well-designed study that actually demonstrates the usefulness of this new compound. However, further analysis by Kryzhanovskaya et al. (56) in comparison to data on file at Eli Lilly demonstrates that the subjects in the study may be at higher risk for development of the metabolic syndrome compared with adults. This finding is an important one in designing the treatment for young people with schizophrenia, and clinicians should be aware of the potential for exaggerated side effects. The results of these studies, which report on the outcome of the olanzapine trial, does not mean that it is the only agent in which there may be an exaggeration of side effects in young people, because other compounds have not been assessed in this fashion.

The atypical antipsychotic medication, quetiapine, has been tested by two different groups to examine psychotic youth. Studies by McConville et al. (57) 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 (58) 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 (59) 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 recent report by Jensen and colleagues (60), quetiapine was compared with olanzapine and risperidone 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 the other hand, quetiapine was very well tolerated in the teenaged patients. As in the previously mentioned analysis of olanzapine data, significant metabolic side effects were noted in the olanzapine arm.

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 (61).

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 (33). As noted earlier, childhood onset and adolescent 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 (63). Evidence for the use of clozapine comes from the NIMH, where Kumra et al. (64) 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 (64).

European studies have reinforced these findings, because Remschmidt and colleagues have reported on 36 schizophrenic patients treated with clozapine (65). 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 (66).

As of the time of this chapter, trials examining the impact of aripiprazole, ziprasidone, or paloperidone have yet to be reported.

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 (62) has carefully reviewed therapy approaches for psychotic youth and noted the added benefit of 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.

Some of our work with families of adolescents with schizophrenia discussed the importance of engagement with families (67). 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.

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 in the last two decades 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 may 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, require much more development in youth.

In closing, recent years have brought increased attention to young people with schizophrenia—especially those in childhood and adolescence. It is hoped that the neuroscience research can advance the field's knowledge regarding schizophrenia as well as providing tangible results regarding the illness and its treatment of youth.

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Part III
Symptom Clusters

23
Mood Disturbances

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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 · Bipolar disorder · Depression · Mania · Mixed state · Mood · Mood disorders · Suicidality

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 emotional expressions that are more enduring. 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 their inward emotional well-being. Each individual has a characteristic pattern of basal affective oscillations that defines their *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 that are sustained conglomerations of affective signs and symptoms typically lasting for weeks to months at a time, and that tend to recur after variable intervals (typically measured in years). Episodes 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 the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (DSM-IV) (1), patients with single or recurrent depressive episodes are said to have major depressive disorder; sometimes referred to as *unipolar disorder*, 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

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age at onset peaks in younger age groups (teenage years 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—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 that 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* by milder periods of frequent highs known as hypomania, and *cyclothymia* by a variability of moods that alternate 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 on 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 having "cyclothymic depressions." Finally, to complicate matters, some unipolar patients should actually be considered "pseudo-unipolar" patients because they descend into major depressive episodes from the higher than normal plane of a hyperthymic temperament (5); another term for this disorder 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 DSM-IV-TR, the term unipolar is avoided, because, with increasing numbers of episodes, many major depressive patients switch to bipolar I or II disorder (6, 7). For all of 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).

TABLE 23.1. The bipolar spectrum.

Bipolar I	Depressions alternating with mania or vice versa
Bipolar II	Depressions interspersed with hypomanic episodes
Bipolar III	Hypomanic switches on antidepressant treatment or other somatotherapy
Bipolar IV	Depression arising from hyperthymic temperament

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 regarding 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 seem 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).

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 older than the age of 40 years, 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

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, alpha-methyldopa, other antihypertensives
Anticancer chemotherapy
Corticosteroids, oral contraceptives
Interferon
Cimetidine, indomethacin
Classic antipsychotics
Anticholinesterase insecticides
Alcohol, barbiturates
Stimulant withdrawal

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 a 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.

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 pains are 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 feeling 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 patient suffers immensely from their inability to experience emotions.

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 thought 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 caused by 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 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.

Similar to 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 patient is a reflection of the painful arousal and prolongs the agony of the patient. Deep stages of sleep (3 and 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 depressive patients, especially those with bipolar tendencies, typically complain of *hypersomnia*, sleeping as long as 12 to 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 depressive patients, 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 patient with insomnia with that of a healthy control subject.

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

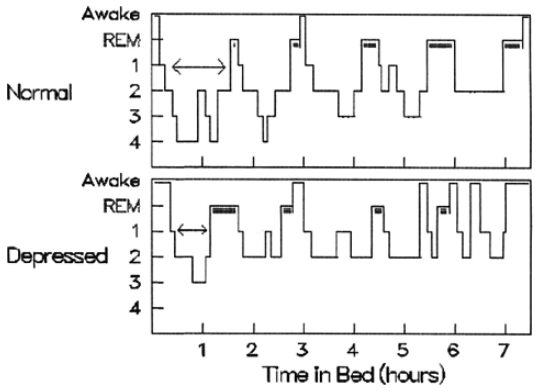

FIGURE 23.1. The sleep histograms of a healthy and a clinically depressed individual.

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 adrenal glands, visible in an abdominal computed tomography (CT) scan (30).

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 depressive patients, especially bipolar patients, psychomotor slowing may in the extreme manifest stupor—the patient is unable to participate even in basic biologic functions such as feeding oneself. History is the most reliable way to distinguish depressive stupor from its hysterical and schizophrenic counterparts. Again, electroconvulsive therapy is often lifesaving

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 morning	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

in such cases, but somatic causes of stupor (e.g., metabolic, neurologic) must first be excluded by appropriate clinical and laboratory evaluation.

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 patient 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 patient's thinking is that they view 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 depressive patients 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 depressive patients may have fleeting auditory or visual hallucinations (e.g., accusatory voices or seeing themselves in coffins or graveyards). All of 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 depressive patients 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 nineteenth century (34). Unfortunately, antidepressants typically improve mood before psychomotor retardation; that is why the recovery period from depression requires vigilance to prevent suicide.

3. The Distinction Between Grief and Melancholia

Depression in its full-blown form is sharply demarcated from the ordinary "blues." The patient and their family will tell the doctor that the depressed state represents a break from their 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 the 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. Because bereaved individuals manifest many depressive symptoms within the first year, how does one decide whether grief has progressed to melancholia, as it does in approximately 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 DST 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 regarding 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).

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 United Kingdom (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 years. Therefore, it is best to consider patients who present with marked anxiety features for the first time after age 40 years 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%. 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, their disorder was 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 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 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 that 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 a family history of bipolar disorder (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 (that sometimes reached full

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

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 also might have affinity to bipolar II disorder (51). In brief, a marked anxiety component in the setting of depression should not be automatically considered "unipolar."

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 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 seems 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.

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 AD (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 seem 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 an 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 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 seem related to temperamental characteristics most affected by lithium salts.

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. In addition, 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 patient's mood as the mood elevation.

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

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).

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 or CDs, 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.

6.4. Cognitive Disturbances

The manic patient 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).

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
Intermorbid	Tempestuous, "supernormal"	Withdrawn or low functioning
Course	Biphasic	Fluctuating, downhill

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 intermorbid 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 caused by 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 the family history is positive for bipolar illness. The following vignette (reprinted from Akiskal and Puzantian, 1979 (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.

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, because 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 electroconvulsive therapy.

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 they 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 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 tends 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

TABLE 23.7. Clinical features of cyclothymic disorder.

General characteristics
Onset before 21 years of age
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

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-1/2*(i.e., between bipolar II and bipolar III).

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 pseudounipolar patients, who are sometimes referred to as having unipolar II disorder, 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 depressive patients 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 years
- 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 regarding the milder end of the bipolar spectrum would be incomplete without mentioning chronically or intermittently hypomanic individuals, who are classified as having hypomanic personality or *hyperthymic temperament* (72). This condition is characterized by intermittent subsyndromal hypomanic features with infrequent intervening euthymia. These patients are typically short sleepers (4 to 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 is 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.

9. Mood Disorder in Different Clinical Settings

This chapter 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 clinical setting, one set of manifestations may dominate the clinical presentation. Common examples include the following:

- Primary care: somatic complaints and substance abuse
- Sleep disorders 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

Because 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 caused by 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?
- In what appears to be borderline character pathology: is it caused by 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 whether the presenting complaints recur in a periodic or cyclic fashion
- To substantiate relatively good social functioning between periods of illness
- To obtain a 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 classic 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), 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, MD

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 virtually always make the illness more severe and disabling, more difficult to treat, and make the prognosis worse.

Keywords Anxiety · Comorbidity · Generalized · Panic · Phobia · Posttraumatic

1. Introduction

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, and 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, or become dizzy, unsteady, perspired, weak, and tremulous. Some feel the need to escape from wherever they are. Others feel immobilized. Not all patients have all of 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, the phobic anxiety–depersonalization syndrome (10), *spasmophilie* (11), endogenous anxiety (12), and finally panic disorder (13, 14). Most newer names have represented delineations of ever more discrete syndromes from earlier, broader categories.

Panic attacks are a common and serious problem. In the United States, 3% of the population has had panic attacks within the past 6 months, and 0.6 to 1% have current panic disorder (15). Rates in Europe are similar (16–19). In medical treatment settings, the proportions are vastly higher (20).

Panic patients have decreased productivity (21) and increased disability (22–24). They experience a diminished quality of life (25). Anxiety disorders impose a severe economic burden on society (26). Panic patients need as much medical care as patients with schizophrenia, major affective disorders, or somatization disorder (26, 27). "...A panic attack is indicative of the almost certain presence of at least one other psychiatric condition" (28) and it is likely to be severe (29,30). Panic patients are likely to have many phobias, including agoraphobia (31, 32). They are likely to become depressed (33). Because of these comorbid conditions, they are at increased risk for suicide attempts (30, 34). Susceptibility seems to be genetically transmitted (35, 36), although perhaps not strongly so (37).

Anxiety is often comorbid with medical illnesses, especially with respiratory disorders, vestibular dysfunction (38); hyperthyroidism and hypothyroidism (39, 40) and other endocrine abnormalities (41–43), lipid disorders (40, 44–46), cardiac disorders, hypertension, gastrointestinal problems,

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and genitourinary difficulties (45); migraine (46), seizure disorder, head injury, and Kluver–Bucy syndrome; and pain (47). Anxiety disorders are highly associated with hyperdynamic beta-adrenergic activity (48, 49).

Patients who experience panic attacks typically go to primary care specialists first (84%). 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.

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 that can cause such symptoms. Before categorizing symptoms as psychiatric, it must first be determined that physical illness is not their sole cause. However, even when a physical illness can be objectively diagnosed, comorbid anxiety will seriously influence severity and outcome.

2.1. Cardiac Diseases

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 (ECG) 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 (50). Typically, anxiety is closely attended to in the aftermath of a heart attack, in attempts to reduce the risk of death during following days and years.

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 (51,52). The episodes are often precipitated by exertion, or by typical anxiety-provoking stimuli, or can appear to be spontaneous. Although there is general agreement that the symptoms of angina pectoris are caused by intermittent restrictions of blood flow to the heart muscle, this is often difficult to establish in individual cases (53). These patients can be mistakenly referred to psychiatrists (54). Laboratory tests will not necessarily differentiate angina from panic. An ECG exercise test can usually establish angina, but often cannot (55). Arteriograms sometimes show narrowing of major coronary arteries, but the degree of narrowing correlates poorly with the severity of angina symptoms.

Microvascular angina overlaps diagnostically with panic disorder (56). Some difficult cases can be documented by 24-hour ambulatory ECG monitoring. To further complicate matters, many cases of cardiac ischemia are "silent" and present no symptoms. A patient might have symptomatic panic attacks and asymptomatic myocardial ischemia.

The symptomatic overlap of angina and anxiety remains considerable. Both are relatively common, and an individual patient might have both diseases.

Cardiologists can diagnose angina pectoris approximately as well as psychiatrists can diagnose panic. The possibility of an anxiety disorder should not be excluded just because someone has assessed the same symptoms as caused by angina. However, many panic patients carry nitroglycerine they do not need, and which might make their symptoms worse. Benzodiazepines have proven useful in the management of angina and even silent ischemia (57). Anxiety symptoms should be treated in patients with chest pain, whether or not there is objective evidence of coronary artery disease (55). Selective serotonin reuptake inhibitor (SSRI) drugs 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.

2.1.3. Cardiomyopathy

Idiopathic cardiomyopathy is highly comorbid with anxiety and mood disorders (58). Alcohol overuse is a common cause of cardiomyopathy.

2.1.4. Mitral Valve Prolapse Syndrome

Mitral valve prolapse syndrome can cause panic attacks indistinguishable from panic disorder. However, most instances of mitral valve prolapse are asymptomatic, and possibly not clinically important (59).

Although many patients with panic attacks have mitral valve prolapse (60, 61), most patients with prolapse do not have panic attacks (62).

2.1.5. Cardiac Dysrhythmias

Cardiac dysrhythmias can cause palpitations, chest pain or discomfort, dizziness, respiratory distress, fainting, and

anxiety (63). 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 ECG changes.

Episodes of paroxysmal atrial tachycardia (PAT) can be mistaken for panic attacks. Measured pulse rates in panic attacks are often normal (64 beats per minute) and seldom exceed 120 beats per minute. In contrast, PAT typically causes a pulse rate above 150 beats per minute.

Fortunately, most dysrhythmias can be documented and characterized by ECG, and identified even by initial computer interpretations. Dysrhythmias can cause anxiety symptoms that might or might not resolve entirely with antiarrhythmic treatment.

Comorbid anxiety symptoms can be treated with SSRIs, 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.

2.2. Respiratory Diseases

Respiratory symptoms are a central part of panic disorder. Patients with panic tend to hyperventilate slightly between attacks (65). Panic patients are more likely than others to develop organic respiratory disease (40).

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. Recurrent pulmonary emboli are expected mainly in individuals with predisposing conditions, such as phlebitis or intravenous drug abuse.

2.2.2. Asthma

Similar to panic disorder, asthma is characterized by episodic attacks of cardiopulmonary symptoms and anxiety. There is a high comorbidity of asthma and panic disorder (66, 67).

Patients who say they have asthma or who are being treated for asthma have an increased incidence of panic attacks (68).

Anxiety disorders increase the history of tobacco smoking, and anxious patients are more likely to report allergies (69): both of these risk factors for asthma are contributors to the association.

Anxiety can precipitate and prolong asthma attacks (70). Panic disorder and asthma are highly associated, and the presence of panic attacks makes asthma's course and outcome worse, and treatment much more difficult (71).

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.

2.2.3. Chronic Obstructive Pulmonary Disease

Generalized anxiety and panic disorders, along with depression, are comorbid with chronic obstructive pulmonary disease (COPD) in as many as half of cases (72,73). Comorbid anxiety significantly diminishes the quality of life of these patients (73).

It is important to assess these patients with respect to anxiety and mood disorders. The SSRI drugs are probably the safest treatment (72).

2.2.4. Pulmonary Hypertension

Panic disorder is comorbid in a minority of patients with pulmonary hypertension, and it increases their functional impairment. Panic disorder in these patients is highly comorbid with depression, which they are even more likely to suffer (74).

"White coat hypertension" (75) is blood pressure elevated by the stressful situation of being in the clinic. Blood pressure results that are more accurate can often be gotten later in the clinic visit, or by the patients' self-measurement at home.

2.3. Neurologic Diseases

2.3.1. Seizure Disorders

"Anxiety, panic attacks, and pseudoseizures may resemble complex partial seizures, and their diagnosis and treatment may be confusing" (76).

Seizure disorders can cause any psychiatric symptom, including any anxiety symptom (77). Some temporal lobe seizures do not progress to generalized convulsions, but present as episodes of anxiety, anger, or other affects (78, 79). Williams (80) found fearfulness to be the predominant emotion in 61% of patients with partial complex seizures. Panic disorder comorbidity is increased by ictal fear (81).

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.

2.3.3. Huntington's Disease

In a minority of cases, before choreiform movements and flaccid paralysis begin, the prodromal phase of Huntington's disease is dominated by panic anxiety (82).

2.3.4. Parkinson's Disease

Panic attacks are common in patients with Parkinson's disease (83, 84), and may be related to motor block frequency and locus coeruleus dysfunction (85). Generalized anxiety disorder (GAD) is increased in dystonia (85).

2.3.5. Sleep Disorders

Approximately a fifth of patients with isolated sleep paralysis have comorbid social anxiety disorder, panic disorder, or GAD (86). Most panic disorder patients have sleep complaints, especially if they have nocturnal panic attacks (87). Disturbed sleep is used in the definitions of GAD and posttraumatic stress disorder (PTSD) (14).

2.4. Endocrine Diseases

2.4.1. Hyperthyroidism

Similar to 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.

However, many panic patients also have abnormal thyroid indices, particularly low thyroid-stimulating hormone (TSH) levels (89). Hyperthyroidism can cause mitral valve prolapse syndrome (90, 91).

Compared with panic disorder, social anxiety and generalized anxiety are more commonly comorbid with hyperthyroidism (92).

Little has been written concerning treatment, 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 antithyroid therapy is effective even when the serum thyroid indices seem satisfactory to the endocrinologist.

2.4.2. Hypoparathyroidism

The symptoms of hypoparathyroidism are those of low serum calcium, and vary considerably (93). 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 regarding what to do if it does not relieve the anxiety.

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 (94). Parathyroidectomy is the definitive treatment.

No study has suggested a role for anxiolytic drugs.

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 (95). Half of pheochromocytoma patients have acute attacks of anxiety, headache, sweating, flushing, and hypertension. Blood pressure is usually also elevated between attacks. 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.

2.5. Intoxications

2.5.1. Caffeine and the Methylxanthines

Caffeine is a commonly consumed stimulant, and too much of it will provoke anxiety symptoms (96). Although 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 GAD are almost identical. In dosages of approximately 700 mg, approximately seven cups of weak American coffee, caffeine will provoke panic attacks in most persons with panic disorder and in many persons without previous panic attacks. Diagnostic evaluation of panic attacks must assess the possibility of caffeine intoxication. Caffeine seems to bind some of the same brain receptor sites as the benzodiazepines, but to exert opposite effects (97). Not all of caffeine's effects are reversed by benzodiazepines (97). Caffeine, theophylline, theobromine, and related methylxanthines are found in coffee, tea, cola, and many other carbonated drinks, energy 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 and panic 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.

2.5.2. Yohimbine

Yohimbine has been used to produce penile erection, but it also can produce extreme anxiety (98). It produces panic 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 might find its way into various "herbal Viagra" products, and, thus, might have been taken unwittingly in patients presenting with extreme anxiety.

2.5.3. Heavy Metals

Heavy metal poisoning can cause a complex mixture of somatic symptoms and anxiety. "Hatter's Madness" (99) is best documented, and causes symptoms including anxiety, phobic avoidance, tremor, weakness, excessive sweating, decreased attention, and agitation (100).

2.5.4. Amphetamines, Cocaine, and Stimulant Abuse

Persons who use amphetamines or cocaine expect to become euphoric, energetic, confident, and accelerated. However, 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 anxiety can also result from occasional use of cocaine (101). Regular cocaine use is comorbid with a threefold or greater risk of panic attacks (102).

The symptoms associated with amphetamine abuse are similar but more severe (103). The individual's anxiety response to amphetamine depends in part in polymorphisms of the adenosine A2A receptor (104).

The amphetamine derivative, MDMA or "ecstasy," can cause anxiety, fear, shortness of breath, nausea, vomiting, bruxism, muscle aches, headaches, and numbess (105). MDMA use is associated with many psychiatric disorders, including generalized anxiety and PTSD (106). In most cases, the anxiety disorder preceded MDMA use (106).

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.

2.5.5. Khat

Khat is yet another botanical stimulant, and its derivative meth-khat is easily synthesized from ephedrine in illicit laboratories. Khat's structure resembles that of an amphetamine, and its stimulant effects are stronger than those of caffeine. Like other botanical stimulants, it produces extreme anxiety in higher doses.

2.5.6. Cannabis

For some people, the depersonalization marijuana often causes is experienced as unpleasant, and provokes anxiety, fearfulness, and agoraphobic symptoms (107).

2.5.7. LSD

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 very safe.

2.5.8. 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 prolapse for echocardiograms. It can cause brief panic or anxiety attacks. Panic patients rarely experiment with it twice. Isobutyl nitrite ("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.

2.6. Combined Systemic Disease (Posterolateral Sclerosis, Vitamin B12 Deficiency)

Combined systemic disease, a vitamin B12 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 anxious or somatoform. In cases with severe pernicious anemia, the patients might hyperventilate and have other anxiety symptoms (109), but mental symptoms can occur without anemia. Documentation of pernicious anemia or low serum B12 levels 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 B12 deficiency causes such a diversity of symptoms that 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.

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. The degree of anxiety in these patients is the best correlate of decreased physical functioning (110, 111).

Chronic fatigue syndrome is highly comorbid with anxiety symptoms, and also with fibromyalgia (112).

Irritable bowel syndrome is highly comorbid with anxiety, depressive, and neurasthenic disorders, which contribute importantly to its severity and poor outcome (113, 114). Finally, these three conditions are highly comorbid with each other (112).

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 (see addendum) (115).

2.8. Somatoform Disorders

Anxiety disorders are highly comorbid with somatoform disorders (116), even with refinements in the diagnostic criteria that have reduced the overlap of defining symptoms (14). In view of all of 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 such as the popular Hamilton (117–119) 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).

However, 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 that 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 B12 deficiency. One might miss a heavy metal poisoning, radiation sickness, or some disease little known in our part of the world.

2.8.1. Malingering

Anxiety symptoms are easy to mimic. Some may feign illness 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.

2.8.2. Drug Seekers

Patients with primary panic disorder and no previous drug abuse are very unlikely to abuse sedatives (120).

However, many polydrug abusers are inclined to include benzodiazepines, especially those with quick onset, such as diazepam and alprazolam, in their smorgasbord.

Although 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 epileptic patients physically dependent on their anticonvulsants, or even those of insulin-dependent diabetic patients. 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 patients experience (121).

3. Treatment

Physicians ideally should give genuine anxiety patients all of 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 abuse euphoriant drugs.

There is general agreement among researchers and academicians that SSRIs are the treatment of choice for anxiety disorders (122, 123). Many studies, typically paid for by SSRI marketers, have shown the SSRI and benzodiazepine drugs equally effective, in that they are all superior to placebo but not significantly different from each other.

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).

It is difficult and expensive to complete a study showing that one effective treatment is superior to another, especially after the passage of considerable time. Such studies would need to be large and long, and no one seems to be interested in funding any of these studies. The high-potency benzodiazepines have long been available as inexpensive generics.

The obvious comparison has not been published, possibly because the result seems so obvious: comparison 1 hour after taking the drug. It has been shown that a benzodiazepine with an antidepressant is effective weeks sooner than an antidepressant alone (124).

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 7 weeks (125, 126).

Some behavioral psychotherapies have shown promise in panic disorder. Most of panic attacks' physical symptoms, and possibly the attacks themselves, result from hyperventilation (127). Thus, panic patients can be helped by being taught to control their breathing (65).

3.1. Antidepressant Withdrawal

Abrupt discontinuation of SSRI medications can cause a rebound in the symptoms they had originally relieved (128).

Although tricyclic antidepressants are now rarely prescribed, their abrupt withdrawal can cause an abstinence syndrome of insomnia, vivid nightmares, and extreme anxiety (129).

4. Alcoholism

Alcohol reduces anxiety initially, but prolonged use increases anxiety. Anxious patients can experience severe rebound anxiety the day after moderate drinking. Their rebound after 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. However, 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 (130, 131). 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 (132). 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 antipanic drugs are not needed (133).

If a patient has panic disorder that has clearly preceded alcohol abuse, the panic disorder might have caused the alcohol abuse.

Prescribing potentially addictive antipanic drugs to these patients poses an obvious risk, but, typically, they report that 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. In fact, a diagnosis of anxiety disorder greatly increases the probability of a drinking relapse (134).

Table 24.1 summarizes physical illnesses causing anxiety symptoms.

TABLE 24.1. Physical illnesses causing anxiety symptoms.

Cardiac
Myocardial infarction
Angina pectoris
Microvascular angina
Congestive heart failure
Paroxysmal atrial tachycardia
Cardiac dysrhythmia
Anemia
Mitral insufficiency
Pulmonary
Pulmonary emboli
Asthma
Endocrine
Hyperthyroidism
Hypoparathyroidism
Hypoglycemia
Pheochromocytoma
Cushing's disease
Diabetes mellitus
Pancreatic carcinoma
Hypopituitarism
Eosinophilic pituitary adenoma
Thyroiditis
Addison's disease
Infections
Malaria
Viral pneumonia
Mononucleosis
Viral hepatitis
Rheumatic fever
Tuberculosis
Bacteremia
Viremia
Chronic fatigue syndrome
Collagen vascular
Systemic lupus erythematosus
Rheumatoid arthritis
Polyarteritis nodosa
Temporal arteritis
Raynaud's phenomenon
Metabolic
Hypocalcemia
Hypoglycemia
Dieting or fasting
Malnutrition
Low weight
Chronic vitamin deficiency
Neurologic
Grand mal seizure disorder
Partial complex seizures
Migraine
Transient ischemic attacks
Cerebrovascular insufficiency
Brain tumor, especially of third ventricle

TABLE 24.1. (continued)

Cerebral syphilis
Encephalitis
Postencephalitic disorders
Multiple sclerosis
Ménière's disease
Subclavian steal syndrome
Posttraumatic, postconcussive cerebral syndrome
Wilson's disease
Huntington's disease
Parkinson's disease
Combined system disease; posterolateral sclerosis
Myasthenia gravis
Sleep apnea
Sleep terrors
Sleep paralysis
Dream anxiety attacks
Drug-induced, intoxications
Caffeine, theophylline
Amphetamine
Ephedrine, pseudoephedrine, phenylpropanolamine
Cocaine
Cannabis
LSD, psychotomimetic drugs, hallucinogens
Yohimbine
Beta-carboline
Cholecystokinin tetrapeptide
Khat, Methkhat
Tobacco
Withdrawal states
Alcohol
Sedative–hypnotic
Tobacco
Beta blocker
Antidepressant
Nondrug toxicities
Arsenic
Mercury
Lead
Bismuth
Other heavy metal
Carbon disulfide
Organic solvents

5. Other Anxiety Syndromes

5.1. 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, although 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).

5.2. Specific Phobic

Phobias are the most common of psychiatric disorders (140), and are considered normal 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 hunters), or wide-opened spaces (fleet predators). Naïve 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 simple phobic disorders respond not to medication but to behavioral psychotherapy, in which patients progressively accustom themselves to the objects they fear. The other phobias are now preferentially treated with SSRI medications, and few studies have been done to see whether these might yet work for specific phobia. 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.

5.3. Social Phobia, Social Anxiety Disorder

Social phobias were originally narrowly defined as fear of a single, specific social situation, such as public speaking, performing, visiting, using public showers or rest rooms, or eating in public places. These problems were traditionally treated behaviorally, similar to simple phobias, by instructing patients to gradually overcome the fear situation by exposing themselves to it. More recently, SSRI antidepressants (141) have been found to relieve social anxiety disorder. Yet, social phobia remains the most chronic and recurrent of the anxiety disorders (142). It is highly comorbid with the other anxiety disorders, depression, alcoholism, and drug abuse (142).

Agoraphobic patients usually have multiple social phobias. The distinction between mild agoraphobia and severe social phobia can be difficult to make. Social phobias begin at younger ages, occur more in men and in higher social classes, and are less likely to be related to distance from home or to crowded surroundings (143). Social phobics are less generally fearful, less obsessive, and their symptoms are less likely to fluctuate over time, but their main phobic symptoms overlap considerably with those of agoraphobia (144).

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). SSRI combined with benzodiazepine has been shown very effective (147,148), although the improvement is more gradual for social than for generalized anxiety. SSRI monotherapy works almost as well (149, 150), the difference being too small to document except in studies that are large and long.

5.4. Agoraphobia

Most simply, agoraphobia is a fear of leaving home, particularly alone. Most panic disorder patients have multiple phobias, including agoraphobia. Conventional wisdom (151) 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, whereas those not associated with agoraphobia are more likely to include dyspnea and dizziness (152).

Up to half of agoraphobic patients do not have panic attacks (153). Those with panic attacks are more likely to seek treatment, whereas those with uncomplicated agoraphobia simply stay home. Uncomplicated agoraphobia could resemble other phobias in being a residual childhood instinct, because leaving home alone was and is dangerous for a child.

Agoraphobia without panic attacks may not differ fundamentally from simple phobias. It was previously thought that agoraphobic women were particularly likely to tolerate unsatisfactory marriages. A controlled study has shown this not to be so (154).

Agoraphobia was long thought resistant to psychotherapy, but recent studies have changed this view. Simple in vivo exposure can work as well for agoraphobia as for simple phobia (155). Marks (156, 157) maintains that therapist-aided exposure is effective and medication ineffective in agoraphobia.

Treating agoraphobia with panic attacks, Zitrin et al. (158, 159) have found medications effective and self-exposure homework superfluous, because once panic attacks are blocked by medication, agoraphobic patients are no longer afraid to leave home. In cases in which antidepressant medication is effective, psychotherapy has no immediate additional benefit (160). Each form of therapy seems effective as long at it is applied; imipramine (161), clonazepam (162), in vivo exposure, or applied relaxation (163). An advantage of the psychotherapies is that they can be continued by patients on their own (164).

5.5. Homophobia

Homophobia is not, as yet, an official psychiatric diagnosis, as homosexuality once was. (DSM-II; 1968) (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 do not see it much any more; other more current horrors have taken its place.

5.6. Posttraumatic Stress Disorder

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, and abused children. American diagnostic convention emphasizes the anxiety aspects of PTSD, whereas other countries consider changes that occur in mood or even personality.

In PTSD, anxiety symptoms are attributed to previous terrible or at least somewhat unpleasant experiences. The severity of the trauma seems less important than originally presumed (13). Yet, 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 (165). PTSD is highly comorbid with psychiatric and medical conditions, poor health, and a decreased quality of life (166).

Antianxiety and antidepressant medications relieve the symptoms of PTSD; antipsychotic medications are less effective (167). Consensus opinion is that the SSRI medications are the first that should be tried (168).

5.7. Obsessive–Compulsive Disorder

There are still a small number of intractable obsessive–compulsive disorder (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 SSRI antidepressants, or more difficultly with clomipramine (169–171).

5.8. Generalized Anxiety Disorder

GAD is the most prevalent anxiety disorder in primary care (172). 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 to be significantly effective (173). Even so, the condition is highly disabling (172).

6. Depressive Disorder

The author grandiosely considers his own observational work (174) to be of pivotal importance, although others (175–178) published first, and more recent and rigorous studies now deserve all of the citations.

Every anxiety disorder 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 (179–185). Comorbid PTSD has similar adverse effects on depression (186).

7. Bipolar Disorder

Anxiety disorders are more associated with bipolar than with unipolar disorder (187). Anxiety disorders (188), especially generalized anxiety and social phobia (189), are associated with poor bipolar disorder outcome.

8. Psychoses

Panic attacks during adolescence are a risk factor for psychoticism in young adulthood (190). Psychotic affective disorders are highly comorbid with anxiety disorders and stimulant abuse (191). The same is true of non-affective psychosis (192) and schizophrenia (193, 194).

Schizophrenia is associated with anxiety disorders, including social phobia, OCD, GAD, panic disorder, specific phobia, PTSD, and agoraphobia. Even in schizophrenia, anxiety symptoms make the illness worse (195).

Psychotic symptoms suggesting schizophrenia and panic attacks also occur transiently in patients meeting diagnostic criteria for "hysterical" conversion, somatization and borderline disorders, factitious states and malingering, brief reactive psychoses, *bouffées délirantes* and similar conditions that will not progress to chronic schizophrenia.

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

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Abstract Thought disorder is an important symptom complex in schizophrenia. This chapter defines 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 is discussed.

Keywords Disorganized speech · Language · Negative thought disorder · Positive thought disorder; Schizophrenia

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 on definition, although some consensus has begun to emerge during the past 5 to 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 formal thought disorder, or disorganized speech that is presumed to reflect disorganized thinking.

2. Definition

Kraepelin and other great clinicians of the late 19th and early 20th 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 seems 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 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 very 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

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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 them, 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 they 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 that 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 their 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 caused by an infestation of parasites living in the patient's bed, is this a delusion, a hallucination, or both? (It is probably both). When a patient speaks very rapidly, skips from topic to topic, makes little sense, and admits that their thoughts seem to be occurring too rapidly to control, is this a disorder of thought process or thought form? (Again, it is probably both). Further, some patients may clearly display all four classes of cognitive abnormality, whereas others may display one or two classes. The four types may, in theory, be mutually exclusive, but they may co-occur as symptoms in actual patients.

Other chapters in this book 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).

3. What are the Boundaries of Thought Disorder?

Don't people who are otherwise healthy 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 language in an idiosyncratic and confusing way, relying on punning, word play, 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 regarding 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, the patient's manner of speech, the presence or absence of other symptoms, and 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 their 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 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 healthy people, particularly when they are fatigued or disinhibited, and it may occur more frequently in the conscious productions of artists. Whenever clinicians recognize that they are reading or listening to unusual language and thinking, they must always evaluate it in terms of its context. They 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.

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, because they tend to be referred to by 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 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, whereas 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).

4.1. Negative Thought Disorders

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 13 and the boy 10." "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, interviewers may find themselves frequently prompting the patient to encourage elaboration of replies. Doing an interview to evaluate a patient with poverty of speech can be 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."

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 um, 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."

4.1.3. Blocking

Blocking is interruption of a train of speech before a thought or idea has been completed. After a period of silence that may last from a few seconds to minutes, the person indicates that they cannot recall what they had been saying or meant to say. Blocking should only be judged to be present either if a person voluntarily describes losing their thought or if, on questioning by the interviewer, the person indicates that that was their reason for pausing.

4.1.4. Perseveration

Perseveration 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/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."

4.2. Positive Thought Disorders

4.2.1. Derailment (Loose Associations, Flight of Ideas)

Derailment is a pattern of spontaneous speech in which ideas slip off the track onto another track that is clearly but obliquely related or onto a track 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 other times, 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 their 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."

4.2.2. Incoherence (Word Salad, Jargon Aphasia, Paragrammatism)

Incoherence is a pattern of speech that is essentially incomprehensible at times. The incoherence is caused by 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 seems 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 seem to have some oblique connection with the context. Sometimes "cementing words" (coordinating and subordinating conjunctions such as "and" or "although," 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 very uncommon. It may sound very 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.

Examples: 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 eons 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 knickknacks, these cost thirty to forty dollars to get, a good billfold, or a little stand to put on your desk."

4.2.3. Tangentiality

Tangentiality 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."

4.2.4. Illogicality

Illogicality 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 is 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. Any thing 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."

4.2.5. Clanging

Clanging is a pattern of speech in which sounds rather than meaningful relationships seem 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."

4.2.6. Neologisms

Neologisms 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 caused by a misuse of the accepted methods of word formation. For purposes of clarity, these should be referred to as word approximations. Neologisms are very 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."

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.

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?"

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. Recently, however, Bleuler's beliefs regarding 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 healthy people. Finally, it has been observed that not all schizophrenic patients display thought disorder, thereby raising additional questions regarding its diagnostic specificity.

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

TABLE 25.1. Frequency of types of thought disorder in psychiatric patients.

	Manic patients (n = 32)		Depressive patients (n = 36)		Schizophrenic patients (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%

disorder in the absence of a full affective syndrome is highly suggestive of schizophrenia. These results also indicate the usefulness of subdividing thought disorder into various clinical subtypes.

Follow-up studies also have been conducted 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, although 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 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.

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 central to the definition of schizophrenia. Because the symptoms of schizophrenia are varied and complex, during the past decade, 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, whereas the positive syndrome might 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 *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (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 has 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, recent 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). Although 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. An example of a factor analysis of positive and negative symptoms appears in Table 25.2.

TABLE 25.2. Factor analysis of symptom scores from 207 schizophrenic patients.

Factor	Group 1	Group 2	Group 3
	Negative	Disorganized	Psychotic
Avolition	0.82	0.16	0.01
Anhedonia	0.81	−0.01	0.01
Affective flattening	0.79	0.07	0.18
Alogia	0.73	0.46	0.00
Attentional deficit	0.72	0.21	0.16
Positive thought disorder	0.07	0.86	0.12
Bizarre behavior	0.22	0.70	−0.01
Delusions	−0.03	0.11	0.83
Hallucinations	0.22	−0.02	0.78

From reference (29).

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, whereas 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 to evaluate this possibility.

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 (16). Departing from Kraepelin's separation of schizophrenia, Leonhard presents 16 subtypes. There are six subtypes of catatonic schizophrenia, four subtypes of hebephrenic schizophrenia, and six 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 caused by 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.

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26
Phenomenology of Coarse Brain Disease

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Abstract Two previous chapters on the phenomenology of coarse brain disease are briefly reviewed and important organizing principles are delineated. The central focus of the chapter is on traumatic brain injuries and cerebrovascular accidents. Historically germane dichotomies are discussed (organic/functional; mind/body distinctions) together with the notion of "specific etiology." Certain topics from the earlier chapters are updated; neuroimaging and war-related brain injuries are added.

Keywords Blast injuries · Brain insults · Dementia · Neuroimaging · Organic disorders

1. Introduction

There have been two earlier chapters on the phenomenology of coarse brain disease. The first, authored by Abrams, Taylor, and Sierles (1), focused on the lobes of the cerebral cortex and the distinctive psychiatric symptoms that emerge with respective lobe dysfunctions. Additionally, they presented an excellent discussion on areas of the brain that subserve language and memory functions. They also presented valuable information, still germane, regarding simple, reliable tests that can readily be implemented by physicians for inferences about possible organic involvement. The chapter is rich with "bedside" procedures for screening dysfunctions in each of the cerebral lobes as well as for nonlocalized or so-called soft neurological signs. Therefore, these authors took a practical, localization perspective. In the next edition (1994), Robinson (2) placed emphasis on brain disorders associated with demonstrable structural change, with topics limited to dementia, delirium, mood and anxiety disorders, hallucinations, and delusions. The organization and content of this chapter was geared to disorders commonly seen by psychiatrists in the domains of cognitive, affective, and perceptual disorder manifestations, but with instances in which such disorders are found to have a palpable organic base. A large proportion of the chapter was devoted to neurological underpinnings of depression.

Components of both earlier chapters retain relevance and are recommended reading. Our chapter is meant to supplement and, in some instances, extend the topic of coarse brain disease to areas of current concern to practicing psychiatrists. We will look at the brain largely as an integrated, holistic organ with regard to recent data on the deleterious effects of trauma and disease processes on brain functioning. We question the relevance of the functional/organic dichotomy and the Cartesian separation of mind and body and opine that there is an increasing "blurring" of the distinction between modern psychiatry and neurology. Further, it is axiomatic that brain processes are involved in all psychiatric disorders; the issue is that of Meehl's (3) "specific etiology:" Does an organic cause potentiate all other possible causal factors in relation to psychopathology? We will center our coverage on two fundamental conditions that produce coarse brain pathology, traumatic brain injuries (TBIs) and cerebral vascular accidents (CVAs), and will touch on brain imaging techniques that are of increasing importance in psychiatry. Our emphases are based on the dramatic increase in brain insults, including war-related blast injuries, and advances in understanding of the mediators of the intensity and extension of traumatic and vascular insult effects. We will also present updated information on topics from the previous chapters.

2. Background

The term "coarse brain disease" is somewhat analogous to the now-abandoned *Diagnostic and Statistical Manual of Mental Disorders* (DSM), 3rd edition (DSM-III) concept of "organic mental syndrome," which was rejected by DSM-IV on the grounds that it introduced more confusion than it resolved, and in recognition of the fact that the use of the term implied

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that "nonorganic" mental disorders did not have a biological basis.

Disorders involving "coarse brain disease" are those in which there is demonstrable structural change. They include a bewildering array of neuropathologic conditions ranging from CVA and TBI to Parkinson's disease, Alzheimer's disease (AD), Huntington's disease, seizure disorders, and other, less commonly occurring neurologic disorders. In DSM-IV, they comprise, with the exception of the dementias, the category Axis I secondary to Axis III disorders. This innovation, introduced by DSM-IV as an alternative to the "organic mental syndrome" category, has proven to be somewhat cumbersome in practice because the perfect nosology is yet to be developed. Suffice it to say, psychiatric manifestations can and usually are present in just about any medical or neurological syndrome.

Nevertheless, many of the disorders described in this chapter have traditionally been viewed as belonging to the realm of neurology rather than psychiatry. Although historical considerations are largely discounted by textbook authors, the conceptualization of any field owes less to innovators and more to tradition—accidents of history—than we willingly admit. Since the nineteenth century, psychiatry and neurology classically separated along a "Great Wall" dividing supposedly "functional" from "structural" disorders. Although this separation is as anachronistic as the Cartesian mind/body dichotomy, it still lives and flourishes; it continues to inform academic medical curricula, boundaries between medical specialties, and the economic underpinnings of healthcare ("functional" disorders, falling in the province of "mental health," have traditionally been paid for with public-sector money, "structural" disorders, along with the rest of "physical medicine," have been paid for with private money, such as insurance).

Although disorders of coarse brain disease are traditionally considered the province of neurology, their evaluation and treatment will necessarily largely fall to psychiatrists. All of these disorders present with significant psychiatric and behavioral manifestations, including, but not limited to, depression, psychosis, alcohol and other drug dependence, and personality changes. Indeed, often, the psychiatric and behavioral manifestations constitute the most evident and debilitating aspects of the disease process. It is important to emphasize that all of these disorders can present with a complex mélange of symptoms that cut across diagnostic categories. The brain is complex and every brain injury is different. In some cases—such as severe head injury or CVA—symptoms may be incapacitating and immediate; in others, such as dementia or as the sequelae to neurologic disorders, such as Huntington's disease, Parkinson's disease, or mild TBI, they may not show up for days or weeks or years. They may be intermittent and at least partly reversible, as with seizure disorders, or they may be progressive and irreversible, as with AD.

The scope of these disorders is obviously much too vast to be considered in one chapter; indeed, each of the disorders mentioned could easily command a voluminous textbook unto itself.

It should be mentioned that damage occurring in coarse brain disease is seldom limited to a single region of the brain; thus, the syndromes described tend to be rather eclectic. The etiologies involved can all produce diffuse as well as localized damage.

In some cases, the features of these syndromes are highly characteristic. The hippocampal region in the medial temporal lobe, which is important to human memory functions, is particularly vulnerable to injury through CVAs, anoxia, and encephalitis; injury to the language areas of the left hemisphere are, because of the importance of language to most forms of human intercourse, usually dramatic and so incapacitating as to call forth an immediate flurry of vigorous rehabilitation efforts. Other syndromes, such as those affecting the parietal lobe of the nondominant hemisphere, may be subtle or even silent and go undocumented.

3. Traumatic Brain Injury

Called the "silent epidemic," TBI affects nearly 1.5 million individuals in the United States each year. Of those, more than 1.1 million individuals are evaluated and treated in 435,000 emergency room visits; 235,000 are hospitalized and survive, a number that is 20 times the number of hospitalizations for spinal cord injury (4). Fifty thousand people die from TBI each year, making it currently the fourth-leading cause of death in the United States. Although constituting only 10% of cases, use of firearms account for 44% of TBI-related deaths.

Some 13,000 children receive services for TBI in public schools, and it is estimated that nearly 5.3 million people in the United States live with TBI-related disabilities (4). The impact in terms of human suffering and economic loss is staggering: TBI-related costs to the US economy have been estimated at $56 billion a year (5).

Tragically, these injuries preferentially affect the young. They strike down individuals in the prime of life, and the disabilities, suffering, and costs resulting from TBI carry forward for decades. Adolescents and young adults between ages 15 and 24 years are at highest risk, because of their high likelihood of being involved in vehicular crashes, acts of violence, and sports-related injuries (it is estimated that 300,000 cases of mild to moderate TBI occur each year in sports alone). Alcohol is associated with half of all TBI, involving either the person causing the injury or the one under the influence. Rural–urban populations have consistently demonstrated higher incidence of TBI in rural settings, and residents of rural remote counties have the highest overall incidence of TBI and the highest mortality rates (4).

It is self-evident that behavioral factors frequently contribute to the occurrence of TBI. The involvement of alcohol and other drugs has already been noted, as has the use of firearms. Firearm-related TBI often occurs in the context

of alcohol or other drug use or in individuals suffering from mood disorders. It follows that the effort to decrease the burden of TBI will ultimately involve proactive prevention and treatment of alcohol, drug abuse, and depression (6).

It is seldom appreciated, even by psychiatrists, how frequently novel psychiatric disorders emerge after TBI. In one study of adults enrolled in an adult health maintenance organization, 49% of subjects with moderate to severe TBI showed evidence of psychiatric illness in the year after the brain injury. By comparison, 34% of those with mild TBI, but only 18% in those without TBI, had evidence of psychiatric illness (7). In another study in which patients with TBI were followed an average of 30 years after the injury, the lifetime incidence of Axis I disorders was found to be almost 62%; however, in 48% of patients, the Axis I disorder began after TBI, and the most common disorders were depression and alcoholism (8). TBI has been shown to produce subtle pathological changes in brain tissue predisposing to early onset dementia; a number of studies have shown that it doubles the risk of AD (9–15).

Psychosis in TBI is relatively rare, but failure to recognize it can be devastating, as the following case report illustrates.

3.1. Case Study: TBI Patient with Presumed Psychosis (Sheehan and Thurber [16])

The patient was a 34-year-old white man, living alone in a rural area, who at age 16 years had been involved in a motor vehicle accident resulting in a closed head injury, broken back, and paraplegia. In the course of subsequent treatment, he became addicted to pain medication (subsequently resolved) but presented with increasing disorientation and delusional behavior. He was administered a bewildering array of antipsychotic medications for "schizophrenia" (which was his formal diagnosis), that proved to be ineffective. Because of the patient's history of addiction to prescription drugs and the fact that he resided in a rural area, he was unable to obtain medical care. Over time he would become increasingly paranoid and barricade himself in his apartment, later to arrive in the emergency room, threatening suicide, and be dispatched to the nearest psychiatric inpatient unit.

Usually, these admissions produced only a temporary intermission of his symptoms. However, during one admission, the patient was administered a single-photon emission computed tomography (SPECT) scan that showed a large area of hypoperfusion in the left hemisphere, including almost complete ablation of the temporal lobe together with disruptions of the connections with Broca's area, similar to disconnections found with certain schizophrenic patients (see Fig. 26.1 and Color Plate 5, following p. 650 compared with the "healthy" scan in Fig. 26.2 and Color Plate 6, following p. 650). As a result of the scan, the patient was diagnosed as suffering from "Psychotic Disorder due to Traumatic Brain Injury (PDTBI)" instead of schizophrenia. However, in accordance with protocol, he was sent to a State Hospital for longer-term assessment and stabilization. There, he was diagnosed with "Personality Disorder Not Otherwise Specified" and discharged to his own apartment without medications. Later, he returned to the stabilization unit and the process repeated itself. The next time he was seen for follow-up, and still evincing paranoid delusions, he had attempted to stab himself in the chest, missing the heart but penetrating the pericardium. He deteriorated on the intensive care unit (ICU) and had to be transferred by helicopter to a major metropolitan medical center's trauma unit for stabilization.

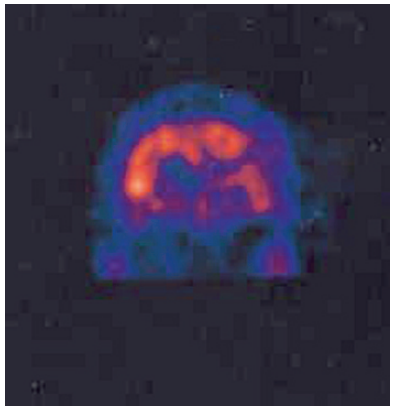

FIGURE 26.1. Temporal lobotomy (*see* Color Plate 5, following p. 650).

We would submit that an essential temporal lobotomy constituted a "specific cause," (see above) and superseded other possible causes vis-à-vis treatment consideration; medications used to treat temporal lobe irritability may have precluded the very adverse outcomes with this individual.

Typically, TBIs damage the axons, affecting myelin integrity and cerebral white matter, resulting in generalized volume reduction. Data on the presumed critical variables in affecting severity of neurocognitive sequelae, length of posttraumatic amnesia, and injury severity, are found to be

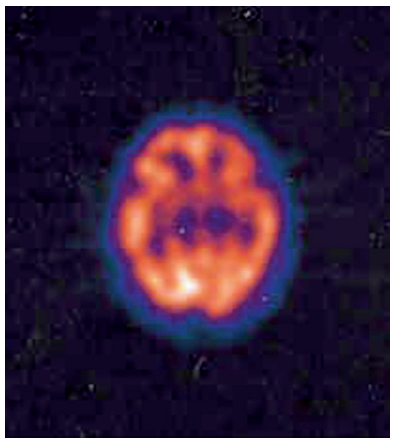

FIGURE 26.2. Normal SPECT scan (*see* Color Plate 6, following p. 650).

inconsistent in the research literature. This is because of factors that mediate the effect of trauma:

- Cognitive reserve. Cognitive reserve is a complicated theoretical construct related to the extent of premorbid intellectual capacity and educational level. It can involve the notion that brain pathology must go beyond a protective reserve level before clinical manifestations are observed or that the brain has the capacity to "borrow" from this reserve to compensate for the effects of brain insults (17, 18). Bigler (19) has operationalized cognitive reserve in terms of total intracranial volume (TICV). This refers to a sum of whole brain parenchyma (white and gray matter) and total cerebrospinal fluid. A comparison between TICV and ventricle-to-brain ratio (VBR) (a generalized measure of brain pathology) yields a measure of brain atrophy after insults. Kesler et al. (18) found that larger TICV provides greater resilience to neurocognitive deficits after TBI.
- Age. Chronological age is an indirect measure of the adverse impact of processes that affect cerebral integrity over time and make the individual more vulnerable to neurocognitive impairments involving TBI.
- Timing of assessment. There are data that the full intensity and extension of impairment will not be revealed until approximately 90 days after brain insult (20).
- Amount of tissue involved in the insult. Hopkins, Tate, and Bigler (21) investigated the premise that, in the absence of a localized lesion, the amount of tissue loss is a cardinal consideration in the adverse effects of both TBI and anoxic brain injury (ABI). Indeed, with TBI and ABI patients matched on VBI, age, and education, the authors found similar adverse neurocognitive sequelae, such as anomalous attentional processes, executive function deficits, and memory impairments.
- Regarding focal brain injuries, one must consider both structural anomalies and concomitant dysfunctions together with interrelationships of the focal damage that may disrupt the entire system or network in which the specific structure is a part. For example, Bigler et al. (20) reported that specific hippocampal injury or atrophy has only limited predictability on memory functions; one must consider how the specific damage affects functional connectivity in the entire network of brain structures involved in memory.

3.2. Neuroimaging Evaluations of Patients with TBI

Behavioral neurological assessments remain the gold standard for documenting the functional impairments of patients with TBI. However, functional brain imaging studies now provide alternative approaches to appreciating the deficits of these patients. A convincing body of literature has demonstrated that cerebral perfusion and metabolism defects do correlate with functional deficits. Nevertheless, we caution that there is, to date, no brain imaging test for the diagnosis of any specifically psychiatric condition. The exception is "coarse brain disease" in which brain imaging is used to include or exclude gross neuropathology as an etiology or contributor to the patient's symptoms. There are currently several forms of functional neuroimaging, including functional magnetic resonance imaging (MRI) and positron emission tomography (PET). We will limit our discussion to SPECT studies. At present, this method is the most widely available. Although the technology is changing rapidly and other methods have clear advantages, the SPECT approach is not the point of this chapter, and a discussion of functional brain imaging is far beyond the scope of this text.

A number of studies have evaluated the relative effectiveness of imaging techniques—including computed tomography (CT), MRI, SPECT, and quantitative MRI (QMR)—for detecting brain abnormalities in TBI patients (22); unfortunately, most have not incorporated neuropsychological testing into their designs.

MRI and QMR findings seem to relate only modestly to neuropsychological outcome, probably because they mainly provide information regarding anatomy. In contrast to these static neuroimaging techniques, SPECT (despite its rather poor image resolution for anatomic detail) provides an imaging modality based on perfusion of a radiotracer; thus, it demonstrates regional and global cerebral blood flow correlating broadly with metabolic activity and furnishes indications of "function," both regionally and globally.

A number of studies have shown that SPECT is more sensitive than CT or MRI in detecting abnormalities after TBI and that it is able to visualize lesions that are not seen on static neuroimaging; it can also detect abnormalities at an earlier stage after acute TBI than CT or MRI (22, 23). SPECT seems to be particularly sensitive to lesions associated with mild TBI, which are often missed using static neuroimaging techniques (24, 25).

One of the few studies comparing SPECT with neuropsychological test results suggested that SPECT may be a more sensitive index of brain injury than neuropsychological testing, because test findings predicted the presence or absence of regional cerebral blood flow abnormalities on SPECT but SPECT findings did not predict test performance (26).

It should be noted that the pattern of deficits on neuropsychological testing (e.g., relatively greater deficits in verbal than visual memory) is similar in depression/posttraumatic stress disorder (PTSD) and in mild head injury (27). Thus, it is not always easy to determine from neuropsychological testing alone whether a brain injury occurred. In addition, perfusion deficits are often reversible over time or as the result of therapeutic interventions (28). These considerations serve to illustrate the fact that—as with the mind/body dichotomy—the function/structure dichotomy is a misleading one.

In sum, it seems certain that functional brain imaging will become of increasing usefulness in documenting brain

abnormalities related to mild brain insults. Its use will certainly supplement, although it is unlikely to ever supplant, behavioral neurologic examinations of psychiatric patients that can be carried out at the bedside or, more formally, by neuropsychological testing (29, 30). The quality of the assessment is a function of the examiner's ability to observe, elicit, and describe the diverse manifestations of cerebral dysfunction (31).

4. Cerebrovascular Accidents

Cerebrovascular disease refers to any disease process involving pathology of the blood vessels of the brain. The cardinal feature is the stroke, and the sequelae (including specific syndromes, such as the classic Broca's and Wernicke's aphasias, or expressive and receptive aphasias) are usually regarded as the province of neurology and discussed in great detail in neurology textbooks. Stroke is the third leading cause of death in the United States, after heart disease and cancer (and just ahead of TBI). As might be expected, cerebrovascular conditions have dramatic overlaps with psychiatric conditions.

Infarcts involving the middle cerebral artery distribution of the left hemisphere produce the classic aphasias; those involving the middle cerebral artery distribution on the right hemisphere produce more subtle, but still significant, impairment involving primarily spatial orientation, including the awareness of one's own body in space. By contrast, TBI most often produces damage to the vulnerable poles of the frontal and temporal lobes, classically in a coup–countercoup pattern. Dementia of the Alzheimer's type and ABI typically involve diffuse bi-hemispheric damage. Vascular dementia syndromes may result either from large vessel disease with extensive areas of cortical infarction or from multiple subcortical (lacunar) infarctions.

In evaluating cerebral dysfunction caused by coarse brain disease, regardless of the underlying etiology (e.g., TBI versus stroke), it is necessary to describe and catalog individual manifestations of that dysfunction, and to perform specific bedside testing techniques (see reference (1) for elaboration).

4.1. Brief (and Simple) Review of Brain Regions Involved in Psychiatric Disorders

It is of interest to note in the historical context that the study of "coarse brain disease" was key to the establishment of the anatomic localization of cerebral functions, beginning in the 19th century with the celebrated and highly instructive case of railroad worker Phineas Gage and the stroke patients studied by neurologists Paul Broca and Carl Wernicke that defined the expressive and receptive seats of language functions in the left hemisphere of the brain. This kind of neurostructural and neurofunctional data remains essential to the successful decipherment of these syndromes today. Whereas it is important to understand brain structures and their localized processing functions, it is also critical to realize that demarcated pathology in a particular region may be associated with forms of behavioral, cognitive, and/or emotional maladaptation because of functional disconnections between that cortical area and entirely different structures within the network of interconnections.

4.1.1. Prefrontal Cortex

Intact functioning of the prefrontal cortex is thought to be necessary for many higher-order cognitive functions, such as working memory, set shifting, behavioral inhibition, decision making, and cognitive control of behavior. Most studies have focused on skills that have been traditionally related to the more dorsal and lateral aspects of the prefrontal cortex, such as working memory and planning skills. However, the ventromedial prefrontal area relates to (based on brain damage studies) problems in decision making. Malfunctions are associated with many psychiatric disorders, including attention-deficit hyperactivity disorder (32).

4.1.2. Temporal Lobe

The auditory cortex is located in the temporal lobe; structures involved in speech and memory (verbal, episodic, declarative) are also located in the temporal lobe.

4.1.2.1. Amygdala

The amygdala is a complex structure comprised of at least 13 nuclei located in the anterior medial temporal lobe, with extensive connections to many brain regions including the neocortex, hippocampus, brainstem, thalamus, basal forebrain, and claustrum. Damage to the amygdala may result in difficulties in judging the extent to which facial expressions signal fear and other negative emotions such as anger, and, as such, may adversely affect social judgments. Malfunctions in this structure have been implicated in autism spectrum disorders and in disorders characterized by aggression (33).

4.1.2.2. Hippocampus

The hippocampus is a critical structure in memory encoding and retrieval and in learning; it is implicated as a major structure effected by AD and in amnesiac disorders.

4.1.3. Parietal Lobe

The parietal lobe is involved in processing and integration of sensory information. Damage to the left parietal area may result in Gerstman's syndrome (left–right confusion), agraphia, acalculia, and aphasia. Right parietal damage may result in contralateral neglect, constructional apraxia, and anosognosia.

4.1.4. Occipital Lobe

The occipital lobe contains the visual cortex and is involved in visuospatial processing. Dysfunctions of the occipital lobe include color and movement agnosia, agraphia, and alexia.

5. Coarse Brain Injury Affecting Language Functions

Language is primarily subserved by the dominant hemisphere, but the affective components of speech (called prosody) are subserved by the nondominant hemisphere. Speech is localized primarily in the perisylvian areas of the frontal, temporal, and parietal lobes of the dominant (for words and word usage and not the affectivity of speech) hemisphere. Fluency of speech is a function of Broca's area, the frontal cortex, and the supplementary motor cortex. Broca's motor aphasia results from damage to the left posteroinferior region of the frontal lobe (Broca's area). Characteristically, patients with Broca's aphasia, although capable of understanding spoken language, are unable to express themselves fluently. They tend to be dysarthric, frequently dropping small words such as articles and prepositions ("the," "to," "a"). Speech without these small words is called "telegraphic." Sometimes patients with Broca's aphasia are mute, sometimes they are able to express themselves only with affect-laden words (such as profanities) that are accessed via the nondominant hemisphere.

Because of the extent of brain tissue damage associated with most diseases producing Broca's aphasia, problems not directly related to spoken language often accompany it. These abnormalities include ideokinetic dyspraxia of the ipsilateral hand (sympathetic dyspraxia), buccolingual dyspraxia (the patient may have trouble puffing out their cheeks, whistling, or blowing out a match), weakness or paralysis of the contralateral extremity, and dysgraphia of the ipsilateral (and sometimes the contralateral) hand (again, the excellent chapter by Abrams et al. (1) is recommended for further reading on this topic).

6. Dementias

Dementia is defined as deterioration in intellectual function. There are two essential features of the dementia syndrome. The first is global impairment of intellectual function. Although the impairment in each cognitive domain need not be uniformly severe, there is nevertheless an impairment in all or nearly all aspects of cognitive function. The second essential feature of the dementia syndrome is that the deterioration of intellectual function occurs in a state of clear consciousness, which differentiates it from delirium (see Robinson (2) for elaboration).

The most common dementias are of the Alzheimer's type and the vascular dementia syndromes. As noted earlier, TBI is associated with increased risk for dementia of the Alzheimer's type, and small subcortical or lacunar strokes are typical of vascular dementia syndromes (although multiple large areas of cortical infarction can also produce such syndromes). In addition, there are a large number of conditions associated with dementia that cannot be fully enumerated here, including demyelinating disorders, such as multiple sclerosis; degenerative disorders with motor symptoms, such as Huntington's or Parkinson's disease; and neoplastic conditions, such as angiomas or gliomas. Further, dementias may be associated with hydrocephalus, inflammatory conditions, infectious conditions, and toxic metabolic disorders (see Robinson (2) for further delineation).

6.1. Alzheimer's Disease: Recent Findings

Recent data on AD suggest that neurofibrillary tangles show a predilection for areas of the brain that involve connections between and among distinct brain structures. In particular, this occurs in the limbic system wherein there is a disconnection between the hippocampus and the neocortex leading to an amnesic syndrome, perhaps the most commonly discussed symptom of the disorder. The greatest impact, and the most thoroughly documented deficiency, is on episodic memory, the memory function related to one's ability to recollect the time, place, and emotionality associated with experienced events (see below). Disconnections also occur in corticocortical pathways, leading to an inability effectively to coordinate information processed in separate cortical regions. For example, Festa et al. (34) reported AD patients to be impaired in sensory integration that involves cross-cortical interactions. Participants were impaired when they were required to infer the direction in the motion of dot displays, a task that placed demands on cross-cortical interactions, which requires a combining of motion and color to perceive the dots in motion.

Whereas memory deficiencies have been well documented, only recently have investigators looked at AD in relation to memory distortions. There is a tendency for people with normal memory functions to misattribute as "true" faulty information with which they have previous familiarity. To participants with a probable AD diagnosis, Mitchell et al. (35) presented a series of recorded (auditory and visually) trivia statements (half factually true, half factually false). Later, the patients were presented with the same statements together with interspersed novel statements. AD participants did not commit the error attribution of "truth" via familiarity, apparently because memory deficits preclude adequate recognition and recall of previous trivia items. In another condition, different trivia statements were presented, some were appropriately cued as "true" others as "false." The participants were asked to remember both the statement and its true or false designation in a subsequent recognition evaluation. Under

these conditions, the participants could prevent an error attribution by recall of the appropriate cues. AD participants were more likely than control subjects to evince misattributional memory distortions.

In addition to neocortical disconnections and memory distortions in AD, there is increasing research interest in cognitive precursors to the clinical manifestations of AD. Backman et al. (36) conducted a meta-analysis of 47 independent studies involving 1,207 preclinical AD cases and 9,097 control participants. These integrated findings suggest that AD patients may exhibit cognitive deficits years before their AD clinical diagnosis. Importantly, areas of the brain that subserve episodic memory (regions of the medial–temporal lobe) may be adversely affected years before reaching the threshold for a clinical diagnosis of AD. Moreover, there seem to be global cognitive dysfunctions in the preclinical phase, including impairments in executive functioning (working memory; planning and execution) and perceptual processing speed. In addition, with reference to the cognitive reserve notion above, persons with greater reserve capacities may not evince clinically significant effects of AD until comparatively elevated involvement of tangles, plaques, and synaptic loss (37).

6.2. Vascular Dementias

Stroke-related dementias are second only to AD as the most common cause of dementia in the elderly and account for as many as 35% of cases of chronic progressive intellectual deterioration (38). This dementia, produced by multiple areas of ischemic injury, is characterized by abrupt onset and stepwise deterioration associated with each subsequent infarct. In addition to this characteristic stepwise course, multi-infarct dementia is also associated with a fluctuating course, because partial recovery occurs over time, but subsequent strokes lead to further deterioration. Multi-infarct dementia is also characterized by relative preservation of personality; when effects are in the left frontal lobe and there is a history of hypertension with focal neurologic signs, depression is a concomitant symptom (see Robinson et al. (39); see also Federoff et al. (40) for discussion of similar findings in patients with acute TBI). The features of the dementia and severity of intellectual impairment depend on the location and especially the volume of the infarcted tissue. Multi-infarct dementia can result from multiple subcortical infarctions, extensive large vessel disease resulting in large areas of cortical infarction, ischemic injury to the deep white matter of the hemispheres (Binswanger's disease) or mixed vascular pathologies.

7. Blast Injuries

As the final topic, we have chosen a type of brain insult that may be unique in recorded history. Unfortunately, as this chapter is being written, American military personnel are involved in combat operations in Iraq and Afghanistan. Because of the nature of this warfare, American and coalition forces as well as Iraqi and Afghan military and civilian populations are subject to large numbers of explosive munitions attacks. These munitions include improvised explosive devices (IED), rocket propelled grenades, car bombs, land mines, etc., which have become the preferred weapons of various insurgent groups when confronting numerically superior forces. American forces, now well protected with body armor and Kevlar helmets, often survive incidents that in the past would have caused fatal penetration injuries. Sadly, many are surviving only to come home with significant disability secondary to blast overpressure injury to the brain. Blast injuries have become very common in military hospitals, with 59% of blast injury victims diagnosed with TBI (41). Brain pathology usually includes axonal damage caused by the great changes in pressure as the blast wave propagates from the explosion. The exact cause of cellular damage in unclear. Excitotoxicity and oxidative stress have been suggested, and axonal damage is often accompanied by hemorrhage and contusion (41). Cerebral infarction secondary to air embolization is also described (42). In a relevant but disturbing study in laboratory animals, Cernak et al. (43) demonstrated hippocampal ultrastructural damage by electron microscopy as well as biochemical changes associated with oxidative stress, even when the animal's heads were protected, again suggesting that helmets cannot offer complete protection from overpressure (Figs 26.3, 26.4). Clinical syndromes of blast overpressure injuries often overlap with or mimic psychiatric syndromes, most notably PTSD, but also depression, anxiety, and attentional disturbances, again underscoring the relationship of brain pathology to psychiatric illness (41).

Tragically, blast injury patients are increasing in numbers on a daily basis and will present challenges to psychiatrists both in and outside the military. Brain damage from blast injury is relatively rare in the civilian population and would be a preventable injury if humans could resist blowing each other up; unfortunately, this seems unlikely (for more information and references, see "blast injury" on the Defense and Veterans Brain Injury Center Website).

8. Summary

The science related to coarse brain disease has resulted in prodigious knowledge of brain structures and localized functions. However, the structures of the brain are interconnected. Interrelations in the entire network of connections are increasingly implicated in an adequate understanding of the concomitants of brain insults. The impact of localized damage may involve a particular structure only as it interacts in a complex system. Our knowledge of these complicated interactions is inchoate; this is an exciting area for future delineation.

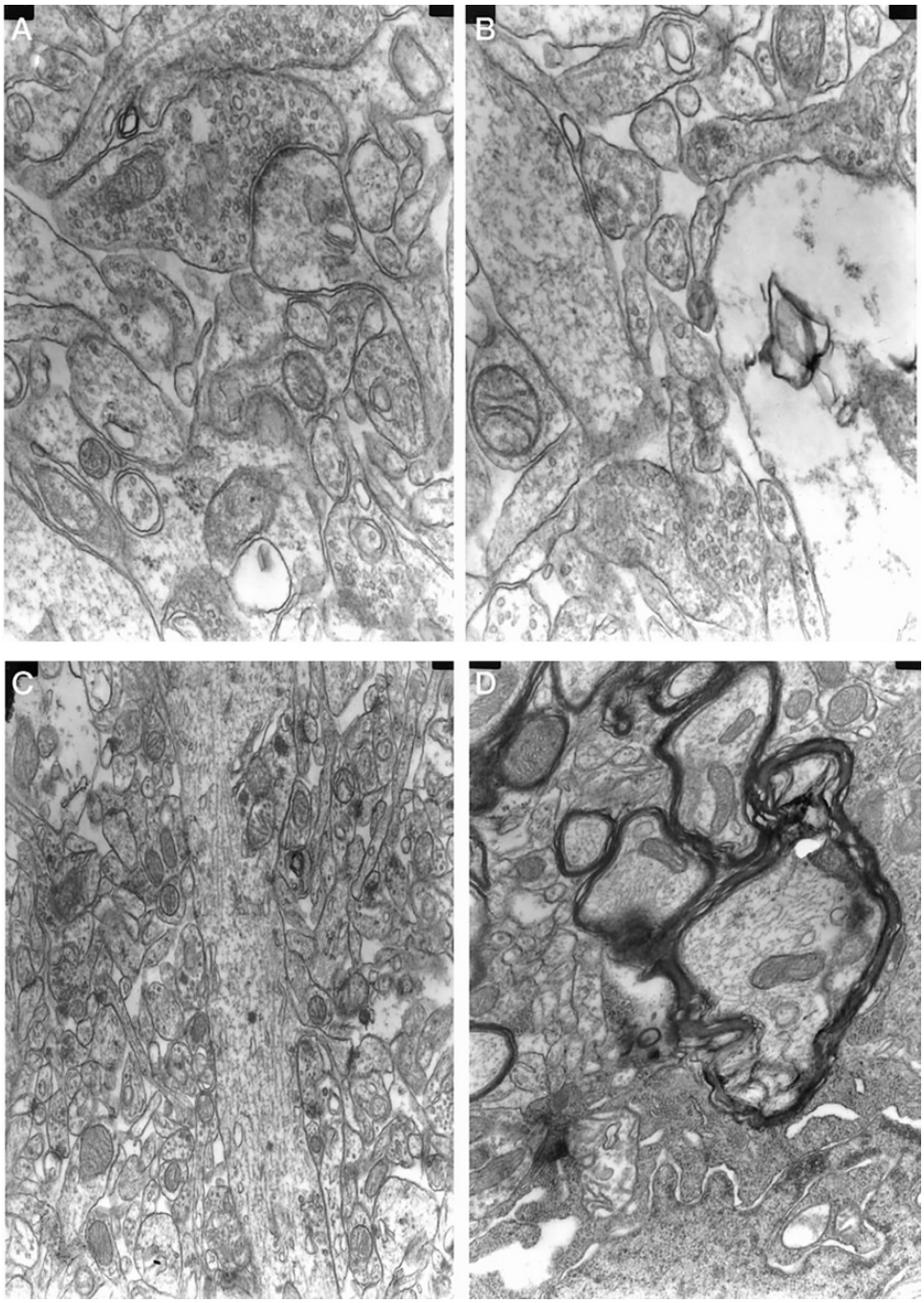

FIGURE 26.3. Electron micrograph of the hippocampus, taken from rats 24 hours (**A** and **B**) and 5 days (**C** and **D**) after whole-body blast exposure. (**A**) Appearance of vacuoles and formation of laminal body. Original magnification, × 25,000; bar = 200 nm. (**B**) Disappearance of cytoplasm and formation of laminal body. Original magnification, × 30,000; bar = 200 nm. (**C**) Appearance of vacuole and formation of dense body in nerve terminal. Original magnification, × 12,000; bar = 500 nm. (**D**) Aerosis of cytoplasm, formation of vacuoles, and local lamination of myelin. Original magnification, × 15,000; bar = 500 nm. Figure reprinted with permission of Lippincott Williams and Wilkins, from reference (43).

We aver that all psychiatric disorders have a basis in some form of brain dysfunction, making an organic/functional distinction irrelevant. However, not all psychiatric disorders have a specific organic etiology (3). Skilled clinicians with sensitivities to manifestations of neurological aspects of psychiatric disorders remain essential; neuroimaging techniques may increasingly be part of a psychiatrist's arsenal. An ostensive overlap in the functions of neurologists and psychiatrists suggest that both subdisciplines might eventually be subsumed under the rubric "clinical neuroscience."

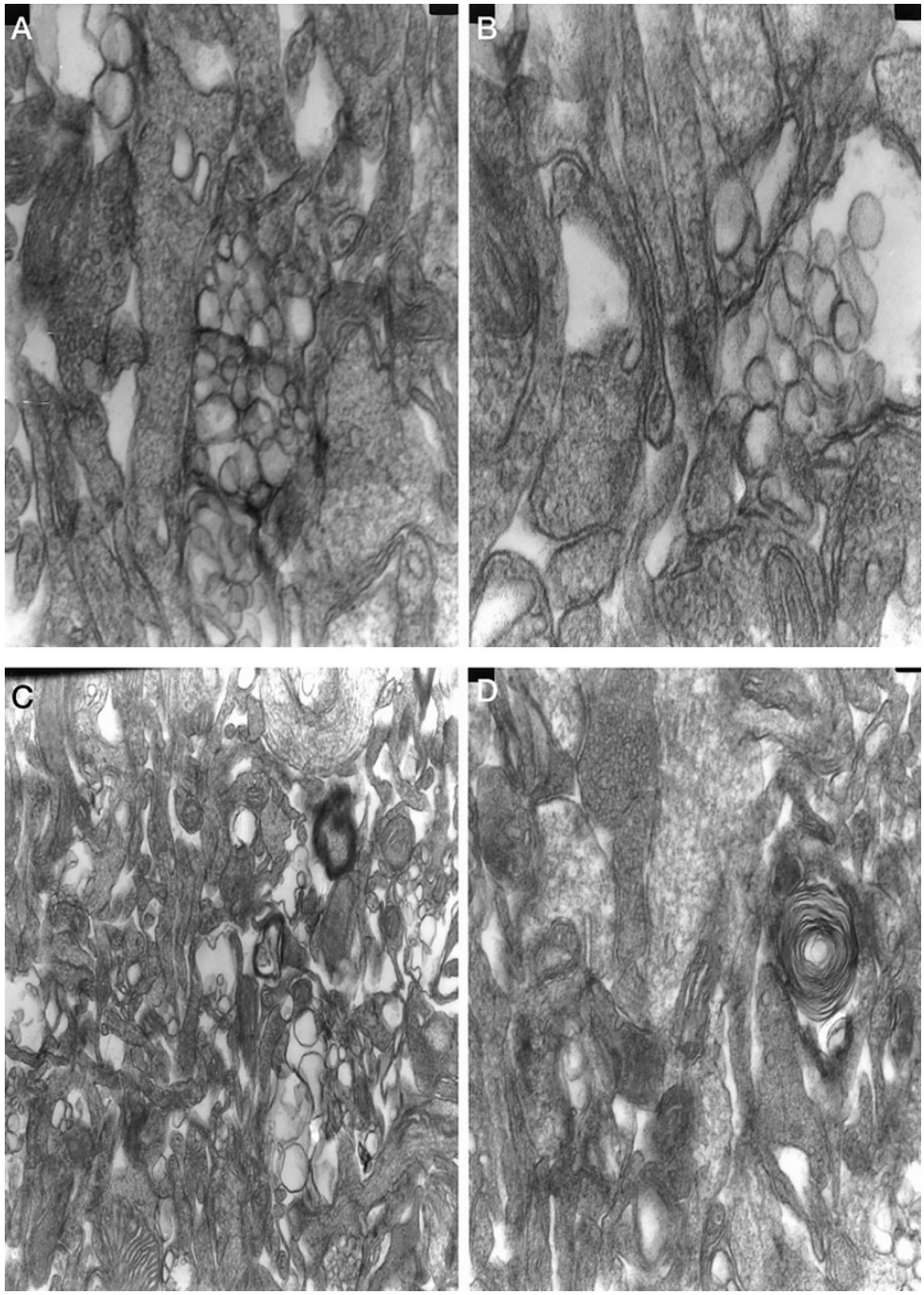

FIGURE 26.4. Electron micrograph of the hippocampus, taken from rats 24 hours (**A** and **B**) and 5 days (**C** and **D**) after local (chest) blast exposure. (**A**) Formation of vacuoles. Original magnification, × 40,000; bar = 200 nm. (**B**) Formation of vacuoles. Original magnification, × 60,000; bar = 100 nm. (**C**) Formation of vacuoles. Original magnification, × 15,000; bar = 200 nm. (**D**) Swelling and thickening of basal membrane, increase of micropinocytotic vesicles, and cytoplasmic extrusion of the endothelial cell. Original magnification, × 30,000; bar = 200 nm. Figure reprinted with permission of Lippincott Williams and Wilkins, from reference (43).

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27
Catatonia in Psychiatric Illnesses

Dirk M. Dhossche, MD, PhD and Lee Elizabeth Wachtel, MD

Abstract Catatonia challenges the validity of modern classification systems by cutting across its proposed boundaries. Contrary to earlier claims that catatonia is restricted to schizophrenia, and soon to be extinct, there is current evidence showing that catatonia is diagnosable in 7 to 17% of acute psychiatric inpatients. A similar proportion of autistic adolescents and adults also meet criteria for catatonia. Sedative treatment and electroconvulsive therapy, the treatments that have historically proven to be effective in catatonia, remain the therapeutic mainstay for catatonia. Evaluation and treatment algorithms that should be helpful when assessing and treating these challenging patients are presented, as well as a GABA-deficit theory of catatonia for guidance of future studies into this syndrome's biochemical correlates. Further studies are needed to optimize the recognition and treatment of catatonia in a wide range of medical and psychiatric patients of different ages.

Keywords Autism · Benzodiazepines · Catatonia · Childhood disintegrative disorder · Children · Delirium · Electroconvulsive treatment (ECT) · Gamma-aminobutyric acid (GABA) · Mood disorder · Movement disorders · Prader–Willi syndrome · Psychomotor abnormalities · Psychosis · Schizophrenia

> 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)

1. Introduction

The study of psychomotor abnormalities in psychiatric disorders requires considerable clinical acumen through direct observation combined with skills to elicit specific symptoms. Although some may interpret Wernicke's quote as hyperbole, the salience of neuropsychiatric impairment manifesting as motor symptoms is nowhere clearer than in catatonia. Interest in this mysterious condition has been rekindled during the last decade. In this chapter, we cover classification issues of catatonia, differential diagnosis, evidence for catatonia as a neurobiological syndrome, a gamma-aminobutyric acid (GABA) deficit theory of catatonia, pediatric catatonia, catatonia in autistic disorders, including childhood disintegrative disorder (CDD) or late-onset autism, and catatonia in Prader–Willi syndrome (PWS). At the end, algorithms for the evaluation and treatment of catatonia are presented.

2. Catatonia in DSM

Catatonia was originally described in 1874 by Kahlbaum as a separate brain disorder with a cyclic, alternating, and ultimately progressive course (2). Kraepelin viewed catatonia as an exclusive subtype of dementia praecox or schizophrenia. In contrast, recent studies show the preponderance of underlying affective disorders, particularly mania, in adult catatonic patients (3–6). In the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition, text revision (DSM-IV) (7), catatonia is a specifier of Schizophrenia, Primary Mood Disorder, and Mental Disorder due to a General Medical Condition. DSM-IV criteria for catatonia are given in Table 27.1, and definitions of specific catatonic symptoms in Table 27.2, with some illustrated by photos from Oswald Bumke's 1924 textbook. Taylor and Fink (8, 9) have recently proposed that catatonia should be viewed as a distinct syndrome in upcoming editions of DSM.

Some consider catatonia as a loose constellation of psychomotor symptoms, that has almost disappeared because of obscure reasons (10) and that is usually associated with schizophrenia. However, empirical findings highlight its increased incidence in psychosis and validity as a syndrome and genetically determined phenotype (11, 12). For example,

From: S. H. Fatemi and P. J. Clayton (eds.): *The Medical Basis of Psychiatry*

TABLE 27.1. DSM-IV diagnostic criteria for the catatonic features specifier (of schizophrenia, primary mood disorder, and mental disorder caused by a general medical condition).

The clinical picture is dominated by at least two of the following:	
1	Motoric immobility as evidenced by catalepsy (including waxy flexibility) or stupor
2	Excessive motor activity (that is apparently purposeless and not influenced by external stimuli)
3	Extreme negativism or mutism
4	Peculiarities of voluntary movement as evidenced by posturing, stereotyped movements, prominent mannerisms, or prominent grimacing
5	Echolalia or echopraxia

in recent samples of acute psychiatric inpatients, the prevalence of catatonia was between 7 and 17% (13,14). Most catatonic patients were actually diagnosed with mood disorders, and many authors link catatonia to manic–depressive illness (4, 15). Twenty-five percent or more of manic patients have enough catatonic features to meet the DSM criteria. More than half of catatonic patients have manic–depressive illness. Approximately 10 to 15% of patients with catatonia meet the criteria for schizophrenia.

In a recent study (16), using a narrow definition of catatonia, i.e., the presence of four or more signs/symptoms with at least one having a score 2 or above on the Bush–Francis Catatonia Rating Scale (BFCRS) (15), 72 subjects (32%) with chronic schizophrenia met the criteria for the catatonia group (mean number of catatonic signs/symptoms = 5.9F2.0; mean sum score of 8.7F3.4 on the BFCRS). The frequency distribution of catatonic signs/symptoms in the catatonic group and in the whole sample was very similar, with mannerisms, grimacing, stereotypes, posturing, and mutism being the most frequent. Catalepsy, mannerisms, posturing, and mutism are the features traditionally associated with catatonic schizophrenia.

In another study (17), a large sample of schizophrenic patients (n = 19,309) was studied. Although the diagnosis of

TABLE 27.2. Definition of catatonic symptoms.

Excitement	Extreme hyperactivity, constant motor unrest that is apparently nonpurposeful
Immobility/stupor	Extreme hypoactivity, immobility. Minimally responsive to stimuli
Mutism	Verbally unresponsive or minimally responsive
Staring (Fig. 27.1)	Fixed gaze, little or no visual scanning of environment, decreased blinking
Posturing/catalepsy (Fig. 27.2)	Maintains posture(s), including mundane (e.g., sitting or standing for hours without reacting)
Grimacing (Fig. 27.3)	Maintenance of odd facial expressions
Echopraxia/echolalia	Mimicking of examiner's movements/speech
Stereotypy	Repetitive, nongoal-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 (Fig. 27.4 and 27.5)	Maintenance of a rigid position despite efforts to be moved
Negativism	Apparently motiveless resistance to instructions or to attempts to move/examine the patient. Contrary behavior, does the opposite of the instruction
Waxy flexibility (Fig. 27.6, 27.7 and 27.8)	During reposturing, patients 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. Afterward, 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 seems 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

FIGURE 27.1. Catatonic staring (from reference 155; p.265).

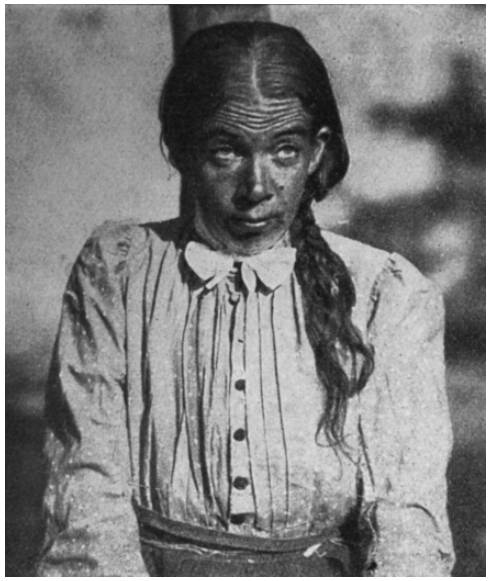

FIGURE 27.3. Catatonic grimacing (from reference 155; p.267).

catatonic schizophrenia dropped from 7.8% in 1980 to 1989 to 1.3% in 1990 to 2001, a possible underdiagnosis of catatonic schizophrenia was found in an independent sample. In a consecutive sample of patients admitted with psychosis, application of a systematic catatonia rating scale showed that 17% fulfilled criteria for catatonia (14).

Together, these studies (16, 17) suggest underdiagnosis and nonrecognition of catatonia both in patients with schizophrenia and bipolar disorder. The reasons are complex, but may include the historical decision to classify catatonia as a type of schizophrenia, the segregation of severely ill psychiatric patients in long-term facilities, and the perceived lack of anticatatonic treatments (13). Another author has posited that, similar to hysteria, changing sociocultural circumstances have suppressed more obvious symptoms of catatonia, such as pervasive negativism, and that the symptom profile has shifted toward more subtle forms that require more clinical acumen to detect (18). This hypothesis assumes that some of the behavioral disturbances in catatonia are not only neurally but also mentally driven. All of these factors may have decreased interest in and recognition of catatonia.

Although there are no controlled treatment studies in catatonia satisfying current standards for evaluating therapies, the literature consistently shows positive effects of anticonvulsant drugs, particularly benzodiazepines and barbiturates, and of electroconvulsive therapy (ECT), regardless of the severity or etiology of catatonia (19–21).

FIGURE 27.2. Catatonic posturing (from reference 155; p.275).

3. Differential Diagnosis

Catatonia needs to be distinguished through a detailed history, clinical examination, and application of diagnostic criteria, from other conditions, syndromes, or disorders featuring psychomotor abnormalities that may overlap with the manifestations of catatonia. The issue of differential diagnosis is separate from the presence in catatonic patients of any underlying psychiatric or medical disorder, or identification of catatonia-inducing substances. Psychiatric and medical investigations are discussed in the section on the evaluation of catatonia. Making an adequate differential diagnosis of catatonia is compounded by the fact that there is no diagnostic biological marker of catatonia, and that the optimal definition of catatonia is not well established. The differential of catatonia

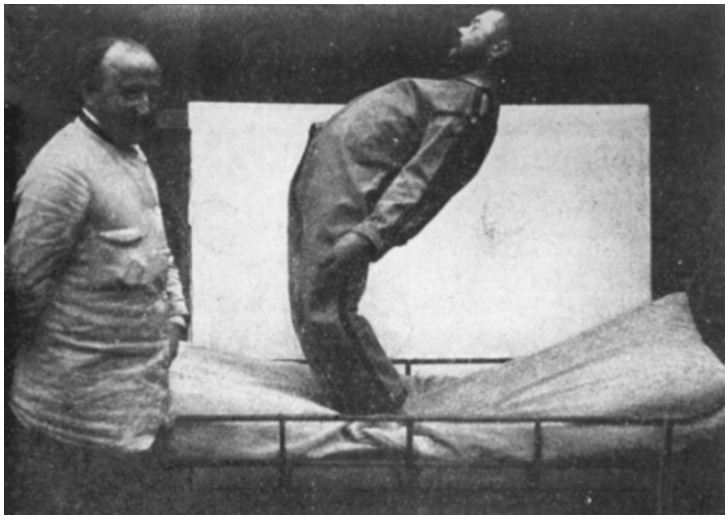

FIGURE 27.4. Catatonic rigidity (from reference 155; p.267).

among hypokinetic and hyperkinetic conditions, syndromes, and disorders is reviewed.

Among the hyperkinetic states, acute dystonia (22) (a sustained muscle contraction, frequently causing twisting and repetitive movements, or abnormal postures), tardive dyskinesia (a hyperkinetic involuntary movement syndrome primarily affecting the mouth, lips, and tongue, but occasionally also the extremities and trunk), withdrawal-emergent dyskinesia (23), and akathisia (subjective sensation of motor restlessness) are medication-induced conditions that may be mistaken for catatonia. Typical antipsychotics are the medications that are usually associated with these movement disorders, but atypical antipsychotics, tricyclic and tetracyclic antidepressants, selective serotonin-uptake inhibitors, monoamine oxidase inhibitors, antiemetics, calcium antagonists, anticonvulsants, stimulants, and a variety of other psychotropics have also been implicated through alterations in central dopamine metabolism (24). Antipsychotics may additionally be a risk factor for the development of catatonia, a subject to be later reviewed.

Tic disorder, Gilles de la Tourette syndrome (characterized by both motor and vocal tics), elective mutism, conversion disorder, and compulsions in obsessive–compulsive disorder (OCD) may also overlap with catatonia. An association between catatonia and some forms of Tourette's syndrome and OCD has been suggested based on cases with comorbid catatonia and Tourette's syndrome (25, 26), and comorbid catatonia and OCD (27). In those patients, tics and explosive verbal behavior resolved with ECT (25, 26). In one case report, obsessive–compulsive behaviors and catatonia developed in a child after a streptococcal infection (28). Antistreptolysin O and DNAse B antibody titers were elevated. The

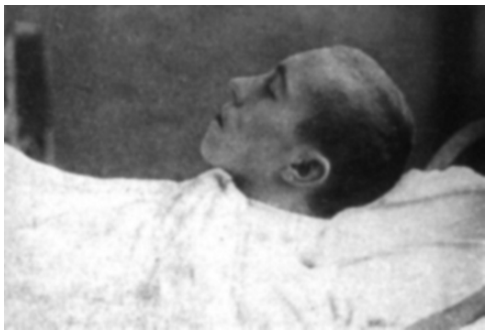

FIGURE 27.5. Catatonic rigidity ("pillow sign") (from reference 155; p.269).

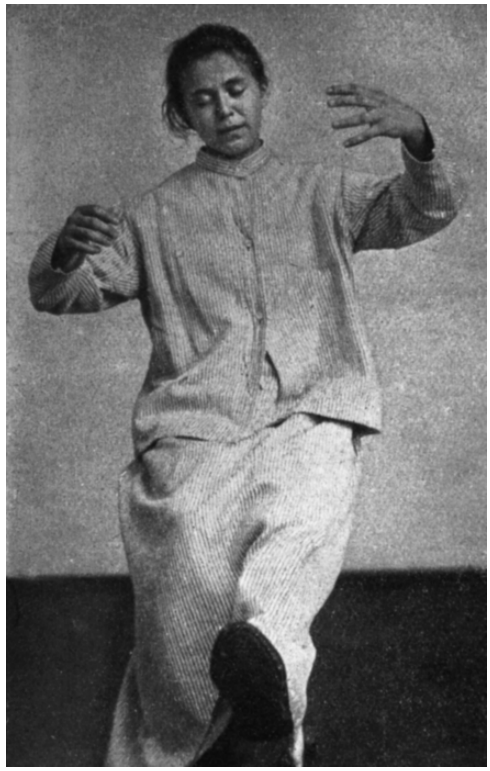

FIGURE 27.6. Flexibilitas cerea (waxy flexibility) (from reference 155; p.271).

FIGURE 27.7. Flexibilitas cerea (from reference 155; p.270).

child improved rapidly with lorazepam treatment followed by plasmapheresis. The authors suggest that catatonia, like OCD and tics, may be another manifestation of pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS). Catatonia also needs to be distinguished from the motor manifestations of hypocalcemia, tetanus, strychnine toxicity, and rabies.

Among the hypokinetic states, pseudo-parkinsonism (characterized by bradykinesia, rigidity, tremor, and gait and postural disturbances singly or in combination) is a medication-induced condition resembling catatonia. Typical antipsychotics are especially prone to cause pseudo-parkinsonism in a dose-dependent fashion, usually within the first month of administration (29). Another group of disorders characterized by varying levels of hypokinesis and muscle stiffness, in combination with altered levels of consciousness, also should be included in the differential diagnosis. The boundaries between catatonia and conditions such as malignant hyperthermia, neuroleptic malignant syndrome (NMS), toxic serotonin syndrome, delirium, stiff-person syndrome, and locked-in syndrome are not well established, however (13). For example, there is discussion in the literature whether NMS and toxic serotonin syndrome truly differ in key aspects with catatonia, or, alternatively, if they should be regarded as medication-induced forms of catatonia (30, 31). The fact that NMS and toxic serotonin syndrome seem to respond to the same treatments as catatonia strengthens the argument of relatedness.

FIGURE 27.8. Flexibilitas cerea (from reference 155; p.272).

In DSM-IV, it is acknowledged that catatonia can occur in association with various medical conditions of infectious, metabolic, endocrine, and neurological etiologies that may also be associated with delirium (7). However, the diagnosis cannot be made if catatonia occurs exclusively during the course of a delirium. The validity of this provision is uncertain because no recent studies that have assessed the importance of catatonia during delirium can be found in the literature. The issue has therapeutic consequences because anticatatonic and antidelirium treatments are different, albeit with overlap. The emergence of catatonia in delirium may also caution against the use of antipsychotic medications, because most clinicians acknowledge that catatonia, at least in some patients, may worsen with administration of typical and atypical antipsychotic medications (31–33). Future trials of lorazepam and ECT treatment, the main treatments for catatonia, in patients with comorbid delirium and catatonia, should be informative about the importance of catatonia in the course of delirium.

Another unresolved classification issue is whether catatonia should be included in the differential diagnosis in patients with coma (complete unresponsiveness) (34), and, in a similar

vein, if stupor or profound unresponsiveness can be the sole presenting symptom of catatonia (34–36). Recent case reports have shown that patients with levels of unresponsiveness similar to those in coma, and without other catatonic symptoms (except resistance to eye opening) responded to ECT (37) and intravenous benzodiazepines (36). Freudenreich et al. (36) describe the challenge of prescribing high-dose benzodiazepines to an unresponsive patient considered to have catatonia. They also recommend the descriptive term "catatonic coma" to replace other terms that imply psychogenesis, such as psychogenic, conversion, dissociative, or hysterical coma, that have no specific therapeutic consequences, once more common medical or neurological causes of coma are excluded.

4. Catatonia as a Syndrome

Fujii and Ahmed (38) have proposed five criteria for a neurobiological syndrome:

- A neurobiological syndrome is a constellation of symptoms that are reliably associated with disturbance that is functional, structural, neurochemical, or neuropathological in a circumscribed structural location or neural circuit.
- Similar neurobiological disturbances (that is, in the location or in the neural circuit) that are secondary to different etiologies would result in similar cognitive or behavioral symptoms.
- Smaller amounts of similar neurobiological disturbances are associated with milder symptoms.
- Additional symptoms such as cognitive, mood, psychiatric, or other associated neurological symptoms are related to other networks simultaneously affected by underlying neurochemical or neuropathological processes.
- The treatment for the neurobiological syndrome is similar across different underlying etiologies that may require separate treatment.

There are several candidate neurobiological syndromes, such as psychosis (e.g., hallucinations and delusions), catatonia, autism, and certain types of depression, e.g., melancholia. Although any attempt for validation of these putative syndromes suffers from our limited knowledge of the relation between brain function and behavior, especially at the cellular and molecular level, this approach has heuristic value for refining current classification systems such as DSM and International Classification of Diseases (ICD), focusing research, and tailoring treatments on an individual basis. Most importantly, clinical presentation would be more firmly tied with neuropathology and etiology than in theoretical models such as DSM or ICD.

Does catatonia qualify as a distinct neurobiological syndrome according to the criteria of Fujii and Ahmed (38)? If so, this would be contrary to Kraepelin's view of catatonia as an exclusive subtype of dementia praecox or schizophrenia, but in line with Kahlbaum's original description of catatonia as a separate brain disorder with a cyclic, alternating, and ultimately progressive course (2). Taylor and Fink (8, 9) have recently made this argument. After reviewing the evidence for the diagnostic validity of catatonia, they concluded (8):

> Catatonia can be distinguished from other behavioral syndromes by a recognizable cluster of clinical features. Catatonia is sufficiently common to warrant classification as an independent syndrome. It can be reliably identified, has a typical course when appropriately treated, responds to specific treatments, and is worsened by other treatments. It is associated with many pathophysiologic processes and most often with mood disorder. These findings, which are consistent with established methods of defining distinct diagnostic groupings, support consideration of catatonia as an individual category in psychiatric diagnostic systems.

In support of the first criterion of Fujii and Ahmed (38), putative neural circuitries for catatonia have been described by Northoff (39) and Carroll et al. (40), involving multiple focal sites such as the anterior cingulate gyrus, the thalamus (mediodorsal), the basal ganglia, the medial frontal cortex, the inferior orbital frontal cortex, and the parietal cortex. Other studies also implicate the pons, upper brainstem, and cerebellum (41). Neurochemical studies supported by functional brain imaging have provided insight into types of cerebral dysfunction responsible for producing the catatonic syndrome (42). Possible neurochemical etiologies for medical catatonias include glutaminergic antagonism, GABA antagonism, serotonergic actions, and dopamine antagonism (43).

In support of the second criterion is the fact that catatonia has been described as a feature of many psychiatric (Table 27.3) medical and neurological conditions (44), including metabolic disturbances, endocrinopathies, viral infections (including HIV), typhoid fever, heat stroke, and autoimmune disease. All of these conditions are commonly associated with both delirium and catatonia. Drug intoxications and withdrawals may also induce catatonia. Neurological conditions associated with catatonia include postencephalitic states, parkinsonism, bilateral globus pallidus disease, thalamic and parietal lobe lesions, frontal lobe disease, and general paresis. Diffuse disease processes associated with medical catatonia

TABLE 27.3. Psychiatric disorders associated with catatonia.

Developmental disorders
Autistic disorder (classic or core autism)
Asperger disorder (high-functioning autism)
Childhood disintegrative disorder (late-onset autism)
Pervasive developmental disorder not otherwise specified (atypical autism)
Prader–Willi syndrome
Mood disorders
Psychosis not otherwise specified
Schizophrenia
Mental disorders caused by a general medical condition
Substance-induced disorders (including neuroleptic malignant syndrome)

support the notion that pathway dysfunction rather than focal (site-specific) dysfunction causes catatonia.

The third criterion for a neurobiological syndrome states that milder neurobiological disturbances cause milder symptoms. Transient drug intoxications with rapid resolution of catatonia support this criterion.

Fourth, catatonia is characterized by concurrent motor, emotional, cognitive, and behavioral symptoms as discussed by Northoff (39). Finally, several studies have found that catatonia responds to benzodiazepines and ECT, regardless of etiology (13). Future research should continue to examine the validity of catatonia by expanding data on the pathophysiology, biochemistry, and treatment of catatonia.

5. Leonhard's Psychomotor Psychoses

Nosology attempts to isolate syndromes that are optimal to guide treatment and prognosis. The classification system of endogenous psychoses of Karl Leonhard (45), elaborated by the group of Helmut Beckmann (46), deserves a special mention. Patterns of psychomotor disturbances and catatonic symptoms are the basis for diagnosis in his system, which is highly standardized and which has shown reliability (46). Diagnostic categories are markedly different from DSM disorders. Among the childhood psychomotor psychoses, Leonhard listed systematic catatonia (chronic catatonic schizophrenia with poor prognosis), motility psychosis (characterized by frequent hyperkinetic phases with psychosis), and periodic catatonia (catatonia with an intermittent course of hyperkinetic and akinetic states) (47). Autism is not specified in this classification.

Recent studies have shown that the age-specific morbidity risk for periodic catatonia in first-degree relatives of probands with periodic catatonia is 27% versus 5% for systematic catatonia in first-degree relatives of probands with systematic catatonia (11). The pattern of familial transmission of periodic catatonia shows anticipation, i.e., the proband's age at the onset of disease was significantly earlier than that of their parent, especially when the afflicted parent was the father (48). Linkage of periodic catatonia to the long arm of chromosome 15q15 has been shown in two studies by the same research group (12,49). Heredity plays a minor role in systematic catatonia (11).

Several DSM disorders may correspond with periodic catatonia that is classified as a subtype of schizophrenia by Leonhard. Taylor and Fink (8) point out that some cases may also fit DSM-IV criteria for bipolar disorder, catatonic subtype, or schizoaffective disorder. Because catatonia seems to be a late-onset complication in autism (50, 51), some patients in this category may also suffer from an underlying autistic disorder. Systematic schizophrenia resembles DSM-IV schizophrenia, catatonic subtype. Family and genetic studies in DSM bipolar disorders do not typically have catatonic subtypes. An association study in patients with affective disorders showed that the distribution of allelic frequencies of a locus on the long arm of chromosome 15q11-13 differed significantly between bipolar patients and control subjects, but not between unipolar patients and control subjects (52). The proportion of bipolar patients with catatonia was not reported. Suspected loci for periodic catatonia and bipolar disorder were found on the long arm of chromosome, although not on the exact same location. The relation between the two loci is unknown.

6. GABA Deficit Theory of Catatonia

A comprehensive biochemical theory of catatonia has proven to be elusive to date (13, 21). In the next few paragraphs, the focus is on abnormalities of GABA function as they may relate to catatonia. The single most important observation leading to the thought that GABA dysfunction plays a role in catatonia is the often dramatic response to treatment with benzodiazepines, i.e., positive modulators of the benzodiazepine/$GABA_A$ receptor complex (19, 53). Other effective treatments for catatonia, i.e., barbiturates, zolpidem, carbamazepine, and ECT (54, 55), also enhance GABA function. Efficacy of serotonergic and dopamine blocking agents in catatonia has been less well documented, but seems less consistent.

Empirical evidence for GABA dysfunction in catatonia comes from one single receptor-imaging study (56), in which a decreased density of $GABA_A$ receptors in the left sensorimotor cortex was found in akinetic catatonia. Other, more circumstantial, evidence is found in a study in which decreased cerebrospinal fluid (CSF) levels of GABA were found in 11 patients with NMS, a condition that may be related to catatonia (57). In this study, levels of noradrenalin were increased, but levels of 5-hydroxyindoleacetic acid (5-HIAA), the main metabolite of serotonin, were slightly, but not significantly, decreased. Further evidence of impaired GABA function in catatonia must await future studies.

If one assumes a central role of GABA dysfunction in catatonia, the scope of GABA functions in the healthy brain should allow the expression of catatonia when deficiencies in GABA function develop. Roberts (58) sees a central role of GABA as neurotransmitter used by neurons that exert tonic inhibition of neural circuits for innate or learned behavioral sequences. In its extreme forms, catatonia is characterized by immobility alternating with purposeless agitation. Although opposite in nature, both behaviors can be viewed as primitive reflexes in response to overwhelming stress or danger that are expressed when innate, genetically preprogrammed neuronal circuits are released from tonic inhibition. Following John Hughlings Jackson's hierarchical concept of dissolution (59), immobility or hyperactivity are then "positive" symptoms caused by the removal of the influence of higher centers. The neuronal circuitry that is involved in catatonia is not well defined, but probably involves frontal cortex, parietal cortex, basal ganglia, and possibly the cerebellum (13).

A few general criteria for any viable GABA theory of catatonia are proposed:

- The theory has to accommodate findings from GABAergic theories of schizophrenia, affective disorders, autism, and PWS, because catatonia occurs in all of these disorders.
- Hypothalamic abnormalities of GABA function should be present and may account for severe autonomic dysfunction in malignant catatonia, a severe type of catatonia with fever and autonomic instability.
- Treatments that relieve catatonia should enhance GABA function, directly or indirectly.
- Genetic studies in catatonia, schizophrenia, affective disorders, autism, and PWS, should provide support for involvement for genes affecting GABA function.

Evidence that GABA dysfunction in catatonia satisfies these criteria is summarized:

- GABA theories have been formulated for schizophrenia (60, 61), psychosis (62, 63), affective disorders (64–66) including bipolar disorder (67), autism (68–70), and PWS (71, 72).
- GABA is a prominent neurotransmitter in the hypothalamus (73). Hypothalamic GABAergic mechanisms are considered important for regulation of stress responses by the hypothalamic–pituitary–adrenal (HPA) (74, 75).
- Most currently used psychotropic medications, including benzodiazepines, antipsychotics (76), selective serotonin reuptake inhibitors (77–79), phenelzine (80, 81), and anticonvulsants, seem to enhance GABA neurotransmission, albeit through different mechanisms. A few studies suggest a direct role of GABA in ECT. In a single-photon emission tomography (SPECT) study, increased benzodiazepine receptor uptake in cortical regions (except temporal cortices) was found 1 week after successful bitemporal ECT (82). In a magnetic resonance spectroscopy (MRS) study, twofold increased brain GABA levels were found in depressed patients after a course of ECT (55). The small number of patients precluded conclusions regarding any correlation between clinical improvement and increased brain GABA levels. Previously, it was reported that CSF GABA levels increased by 50% after ECT (83). In another study, cortical glutamate/glutamine levels in the left anterior cingulum of depressed patients normalized after ECT, but only in responders (84). In nonresponders, levels remained low. Limitations in this study's MRS methodology did not allow obtaining separate measurements for GABA because of overlapping resonances of glutamate, glutamine, and GABA. In a study of plasma GABA levels in depressed patients treated with ECT, plasma GABA levels tended to decrease for approximately 1 hour after ECT (85). Limitations of this study included variable storage times known to increase GABA levels in plasma and CSF and as-needed administration of chloral hydrate, which enhances GABA function similar to barbiturates, during the ECT course.
- There is some evidence that GABA-related genes are involved in affective disorder and schizophrenia. *GABRA5* has been associated with bipolar disorder in two studies (52, 86). In a genome scan of catatonia, a linkage signal in the region 15q11.2-q21.1 (where three GABA-A subunit genes are located) was found (12). No (family-based) gene association studies in catatonia are available in the literature. Findings from a family-based association study in a sample of children and adolescents with childhood-onset schizophrenia (COS) (n = 72) suggested that the gene encoding GAD67 may be a common risk factor for schizophrenia (87). Genetic studies have implicated the involvement of the proximal long arm of chromosome 15 in autism (88–91) and catatonia (12, 49). Three $GABA_A$ receptor subunit genes (*GABRB3*, *GABRA5*, and *GABRG3*) are located at the chromosome location that includes the PWS/Angelman syndrome region. Animal and human studies have suggested a role for these genes in the phenotypic expression of PWS (92) and Angelman syndrome (93, 94). *GABRB3* has been associated with autism in several studies (95–97), especially in patients with increased levels of "insistence on sameness" (a composite score of difficulties with minor changes in personal routine or environment, resistance to trivial changes in environment, and compulsions/rituals) (98) and with savant skills (97). Another cluster of GABA-A receptor subunit genes located on the short arm of chromosome 4 has recently been associated with autism through a family-based association and linkage disequilibrium study (99). In another report, an inversion breakpoint disrupting one of the genes within this GABA-A receptor gene cluster was discovered in two autistic brothers (100).

7. Catatonia in Children

In 1972, Bemporad and Dunton (101) reported the protracted course of illness in a 10-year-old girl and an 8-year-old boy. Both children were diagnosed with catatonia. Their symptoms were similar to symptoms in adult catatonic patients. They reviewed the literature and found only one other case in the literature, which was published in 1926. The earliest description of pediatric catatonia (in a 3-year-old girl) comes from de Sanctis (102), as pointed out by Neumärker (103).

In a subsequent review (104, 105), from 1966 to 1996, 30 cases of catatonia in children and adolescents were found. The mean age was 14.3 years (range, 8–18 years; standard deviation [SD], 2.7 years). There were 18 boys and 12 girls. All 30 cases satisfied DSM-IV criteria for catatonia requiring two of five symptom clusters. Although not all cases had an episode of complete immobility or stupor, all cases had a stupor-like phase with marked reduction of psychomotor activity. Only one case had predominant excitation. Two cases showed mixed features of retardation and agitation. Rates of individual catatonic symptoms in children and adults were similar,

except for urinary/fecal incontinence that was not systematically reported in any of the adult studies. Incontinence is not a DSM-IV symptom of catatonia, but is frequently reported, at least in children and adolescents. Diagnostic distribution was also similar with a preponderance of underlying neurological conditions and affective disorder.

Antipsychotic treatment was implicated in one case. Indeed, antipsychotic treatment is considered a risk factor for catatonia in all age groups, especially if typical antipsychotics are administered in high doses (13, 33). The acute onset of fever, autonomic instability, rigidity, and changes in mood and alertness after administration of antipsychotics are cardinal symptoms for NMS. This constellation of symptoms was described soon after the introduction of antipsychotic drugs (106). However, a similar syndrome was described before the introduction of these drugs and was referred to as lethal or malignant catatonia. The malignant form of catatonia is acute in onset, systematically devastating, and associated with fever and autonomic instability. These patients look as if they have an infectious disease, particularly an infectious encephalopathy. No specific infectious process is usually found. Some are considered to suffer from a coma of unknown etiology. NMS and malignant catatonia overlap considerably, and some have concluded that NMS is an example of malignant catatonia triggered by exposure to antipsychotic drugs (30, 32, 107). The argument is supported by studies that show that laboratory abnormalities are the same in both conditions and, most importantly, that treatments for malignant catatonia, i.e., ECT and benzodiazepines, are equally effective in NMS (31, 108, 109).

What can be concluded from the sparse literature? First, a few studies suggest that the prevalence of catatonia is underestimated. For example, more than one third of children (12 of 38 children) with schizophrenia had catatonic symptoms (110). In a clinical survey of child and adolescent psychiatric outpatients, 5.5% of the sample and 17.7% of the patients with affective and non-affective psychotic disorder met DSM criteria for catatonia (111). Second, despite concerns regarding the small number of cases, varying quality of the reports, and publication bias, all reported cases satisfied the DSM-IV criteria. Symptoms in childhood and adult catatonia are similar. These findings support the validity of childhood catatonia. Third, catatonia in children and adolescents was associated with a variety of psychiatric and medical conditions, including mental retardation and autism. Fourth, no biological or genetic marker for childhood catatonia is evident, a situation similar to that in adults. Fifth, benzodiazepines and ECT are good candidate treatments for both childhood catatonia and adult catatonia. Although very little is known regarding the use of ECT in adolescents, and (prepubertal) children especially (112), most published cases younger than age 12 years in which ECT was used describe the presence of catatonia (113–115). There is also a recent Dutch case report of successful ECT use in a 13-year-old girl with malignant catatonia (116).

8. Catatonia in Autism

Hallucinations and delusions are relatively rare in people with autism, but there is increasing evidence that catatonia is an important cause of impairment in adolescents and young adults with autism (117). To date, there are two systematic studies of catatonia in autism (50, 51) that show that catatonia occurs in 12 to 17% of adolescents and young adults with autism. There are also personal accounts of people with autism with problems in this realm, as suggested by the following description (personal communication, 2006, Coral Hull):

> I used to experience catatonic episodes in my early to mid twenties to the extent where I would stop moving. They would either come on gradually, slowly shutting down my ability to think, speak, and move or they would be sudden such as my body freezing when involved in a decision making process that my brain was unable to handle. Asking me something as simple as whether I wanted pepper or salt on my meal could have me stop moving in a haze of confusion and immobility where I became a statue. Sometimes I was able to make decisions and other times I was unable to.

Such accounts need to be interpreted within the limitations of self-reporting, but, if studied in conjunction with concurrent clinical–observational data, may be valuable for patients and clinicians alike.

In the study of Wing and Shah (50), 17% of a large referred sample of adolescents and young adults with autism satisfied modern criteria for catatonia. A semistructured interview was used to collect information from parents or other caregivers. Patients were diagnosed with catatonia when an exacerbation of certain behavioral features occurred in sufficient degree to interfere with everyday functions of self-care, education, occupation, and leisure. Essential features of catatonia were increased slowness affecting movements and verbal responses, difficulty in initiating and completing actions, increased reliance on physical or verbal prompting by others, and increased passivity and apparent lack of motivation. Other associated characteristics were reversal of day and night, Parkinsonian features (tremor, eye rolling, dystonia, odd stiff posture, freezing in postures), excitement and agitation, and increase in repetitive, ritualistic behavior.

Wing and Shah further reported that 30 individuals with autism aged 15 years or older met criteria for catatonia. Classic autistic disorder was diagnosed in 11 patients (37%), atypical autism in 5 patients (17%), and Asperger disorder in 14 patients (47%). All of those with catatonia were aged 15 years or older. None of those younger than age 15 years had 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 years. 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. Referred patients with catatonia were significantly more likely than patients without catatonia to have had impaired language and passivity in social interaction before the onset of catatonia.

In the second study (51), 13 (12%) of 120 autistic individuals between the ages of 17 and 40 years (mean age, 25.5 years) had clinically diagnosed catatonia with severe motor initiation problems. Another four individuals had several catatonic symptoms but not the full syndrome. Eight of the 13 individuals with catatonia suffered from autistic disorder; the remaining 5 individuals were diagnosed with atypical autism. The proportion of those with autistic disorder that were diagnosed with catatonia was 11% (8/73). Fourteen percent of those with atypical autism (5 of 35 patients) had catatonia.

There are a few important limitations of these two studies. Important variables such as family history and treatment were not recorded. The authors in both studies did not use DSM-IV criteria for catatonia. However, their definition of catatonia included several DSM-IV core symptoms, including severe psychomotor retardation, decreased verbalizations, posturing, and agitated episodes. The high prevalence of catatonic symptoms in autism suggests an intricate, but unaccounted for, relationship between autistic and catatonic symptoms.

An increasing number of case reports and case series of catatonia in autism satisfying DSM criteria of catatonia (118–128) have been published during the last 15 years. There is considerable overlap of psychomotor symptoms between the two disorders, e.g., muteness, echolalia, stereotypical movements, and other psychomotor peculiarities (129). The diagnosis of catatonia in the published cases was made based on significant worsening of these symptoms and emergence of other catatonic symptoms. Some of the authors report that patients responded to treatment with lorazepam, the benzodiazepine most often used, and/or ECT. It should be noted that none of these studies was controlled and the number of cases was small.

Autism should be considered as the underlying condition in patients presenting with catatonia, especially in those with histories of developmental problems. Psychiatrists working with adults are usually much more familiar with schizophrenia and other psychotic disorders than autism. Therefore, catatonia may be misdiagnosed as a feature of schizophrenia, and any underlying diagnosis of autism may be missed, leading to possible suboptimal treatment of both catatonia and autism.

9. Catatonia and Childhood Disintegrative Disorder

An important clinical implication is the need to assess catatonia amid severe regression of unknown cause in prepubertal children, because effective anticatatonic therapies become a treatment option once catatonia is diagnosed. Massive regression, characterized by loss of language, social skills, adaptive behavior, play, bladder or bowel control, and motor skills, in prepubertal children, followed by an autistic state is the hallmark of childhood disintegrative disorder (CDD). The symptom overlap between autistic regression in CDD and catatonia has been noted, however, direct assessments of catatonia in children with CDD are not found in the literature. No ECT use in children with CDD has been reported.

CDD is considered rare, with a pooled estimate across four surveys of 1.7 cases per 100,000 subjects (95% confidence interval, 0.6–3.8 per 100,000) (130). However, it is also likely that an unknown number of cases are not reported because neurologists and other pediatric specialists, who are not familiar with the psychiatric classification of CDD, label this condition differently, e.g., as encephalopathy or encephalitis. Textbooks describe CDD as sometimes associated with known medical conditions but usually no clear cause is found. Deterioration occurs over the course of weeks or months. Residual symptoms include impaired social interaction, restricted language output, and repetitive behaviors. Follow-up studies have suggested that older age at onset of autistic symptoms, as in CDD, may be associated with a worse outcome (131). There is no recommended treatment. CDD and childhood catatonia are both poorly studied and probably poorly recognized. The presence of catatonic symptoms should be assessed in children with suspected CDD during the phase of massive regression (70). Lorazepam and/or ECT should be considered once the diagnosis is confirmed.

10. Catatonia in Prader–Willi Syndrome

Prader–Willi syndrome (PWS) is a genetic disorder characterized by hypotonia at birth, small hands and feet, almond shaped eyes, hypogonadism, short stature, and diabetes (132). Most patients exhibit mild to moderate mental retardation and obesity. Obesity starts in infancy and is accompanied by compulsive eating. The prevalence is estimated at one in 16,000 to 25,000 live births (133–136).

This multisystem disorder occurs in all races and both sexes and arises from the lack of expression of genes on the paternally derived chromosome 15q11-13. Candidate genes for PWS in this region are imprinted and silenced on the maternally inherited chromosome. The genetic defect underlying PWS is the absence of expression of one or more genes of paternal origin located on the long arm of chromosome 15 (15q11-13). Several genetic mechanisms have been associated with PWS, mainly paternal 4-Mb deletion (in ∼60% of cases) and maternal uniparental disomy (UPD) (in ∼25% of cases) (137). In a small number of patients (3%), imprinting errors are found because of either a sporadic or an inherited microdeletion in the imprinting center. There is a paternal chromosomal translocation in 1% of the cases. Imprinting

occurs partly through parent-of-origin allele-specific methylation of CpG residues, which is established either during or after gametogenesis and maintained throughout embryogenesis. Alternatively, if the deletion is maternal or there are two paternal copies of chromosome 15q, another syndrome is found, i.e., Angelman syndrome, characterized by severe mental retardation, attention deficit, inappropriate laughter, ataxia, jerky gait, epilepsy, sleep disturbances, and craniofacial abnormalities (138).

Recent studies have shown that compulsions (132, 139) and psychotic disorders (140, 141) are associated with PWS. Compulsive behaviors in PWS are autistic-like and include insistence on sameness (142), perseveration, and ordering. Hand washing and checking, i.e., symptoms that are typically found in OCD, are infrequent in PWS. Negativism and stereotypic movements of the self-injurious variety, particularly skin picking and scratching, have also been identified in PWS (143). Various psychotic symptoms, including paranoia, hallucinations, and bizarre behavior, have been reported in PWS patients, usually in combination with affective symptoms (140). The acute onset and mixture of affective and psychotic symptoms suggest an atypical form of psychosis.

PWS patients with UPD seem particularly prone to develop psychosis (141, 144, 145). This suggests that an abnormal pattern of expression of sex-specific imprinted genes on 15q11-13 is a risk factor for psychosis in PWS. Superior visual recognition memory is another feature in PWS that has been associated with maternal UPD (146). The genes involved in the development of psychosis and superior recognition memory in PWS are unknown.

There is one detailed description in the literature of acute, full-blown catatonia that developed in an adolescent with PWS and that responded to lorazepam treatment (105). Catatonic symptoms have been described in other patients with PWS, but a formal diagnosis was not made. For example, Clarke (140) reported an acutely psychotic PWS patient with significant psychomotor retardation, refusal of food and fluids, and negativistic behavior. Abe and Ohta (147) described an adolescent with PWS who developed stupor, pallor, and delusional thinking. Bartolucci and Younger (148) observed, in four of nine youngsters with PWS, discrete episodes of a refusal–lethargy syndrome, characterized by akinesis, refusal of foods and fluids, incontinence, and self-neglect, which occurred independently from psychotic episodes and lasted weeks up to several months. These descriptions suggest the presence of catatonia. Catatonia might have gone unrecognized, because some catatonic symptoms are transient and need to be elicited by trained clinicians. Systematic studies are needed to assess the prevalence of catatonia in PWS. The clinician should consider a diagnosis of catatonia in people with PWS with onset of psychosis and psychomotor abnormalities, and implement effective anticatatonic treatments (149).

11. Evaluation of Catatonia

In Fig. 27.9, an evaluation algorithm for catatonia is presented.

Catatonia should be considered in any patient if there is an obvious and marked deterioration in psychomotor function and increase in unresponsiveness compared with previous levels. This should prompt a thorough clinical assessment. Physical examination and laboratory investigations are dictated by clinical assessment. Infectious, metabolic, endocrinological, neurological, and autoimmune diseases have been associated with catatonia and must, therefore, be excluded. For an in-depth review, we refer to two recent publications on this subject (13, 150).

All prescribed medications should be evaluated for their potential to induce catatonic symptoms because many medical and psychiatric medications can cause catatonia or catatonia-like conditions (13, 151). Antipsychotic agents should be discontinued because they are contraindicated in patients who exhibit the signs of catatonia because of the reported increased incidence of malignant catatonia or NMS in patients with incipient signs of catatonia. When the catatonia is resolved, antipsychotics may be useful for select indications, but any reemergence of catatonic symptoms should prompt discontinuation.

Illicit drugs (PCP, mescaline, psilocybin, cocaine, opiates, and opioids), disulfiram, steroids, antibiotic agents (ciprofloxacin), and bupropion have also been associated with the emergence of catatonia in case reports. Withdrawal

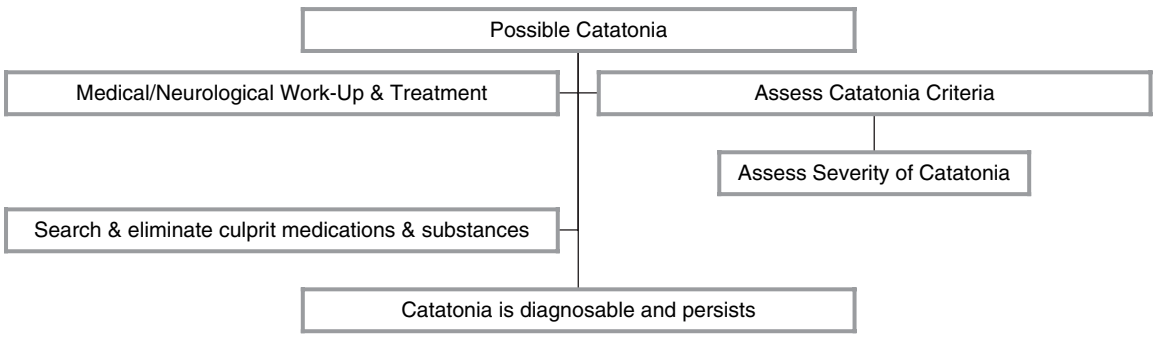

FIGURE 27.9. Algorithm for the evaluation and assessment of catatonia.

of benzodiazepines, gabapentin, and dopaminergic drugs, especially if done rapidly, has precipitated catatonia in some patients (13). As with antipsychotics, antidepressants or any other type of psychiatric medication may be indicated for select indications, when the catatonia is resolved, but reemergence of catatonic symptoms should prompt discontinuation.

Different criteria for a diagnosis of catatonia are used in clinical practice and research. It is unknown how these different criteria compare and which set of criteria is best, because there is no gold standard. Fink and Taylor (13) proposed to base the diagnosis on the presence of immobility, mutism, or stupor of at least 1-hour duration, associated with at least one of the following: catalepsy, automatic obedience, or posturing, observed or elicited on two or more occasions. Alternatively, in the absence of immobility, mutism, or stupor, the diagnosis is based on at least two of the following, which can be observed or elicited on two or more occasions: stereotypy, echolalia/echopraxia, waxy flexibility, automatic obedience, posturing, negativism, or ambitendency. These criteria are less applicable to mute patients, or the majority of autistic patients with baseline symptoms such as echophenomena, stereotypy, negativism, or other psychomotor abnormalities (129). Therefore, diagnostic criteria specific for catatonia in autism have been proposed in which drastically decreased speech replaces mutism and the duration of symptoms is longer (152). A rating scale or checklist may aid the quantification of catatonia. Several scales have been published during the last 10 years and have been discussed elsewhere (13, 21). None of these scales have been applied to autistic populations.

12. Medical Treatment of Catatonia

In Fig. 27.10, a medical treatment algorithm for catatonia is presented based on the cumulative experience in this area (13, 21, 153). The lack of controlled studies must be emphasized, as well as the limited number of published cases of catatonia in select disorders such as autism or PWS.

The algorithm features the lorazepam challenge test for the rapid resolution of acute catatonia. The intravenous administration of amobarbital, lorazepam, or diazepam relieves catatonia in more than half of the patients. Specifically, an intravenous line is established and a syringe containing 2 mg to 4 mg lorazepam in 2 ml (or larger volumes) of solution is prepared, and 1 mg is injected. In the next 2 to 5 minutes, any changes are noted. If no change is observed, the second 1 mg of lorazepam is injected, and the assessment is repeated.

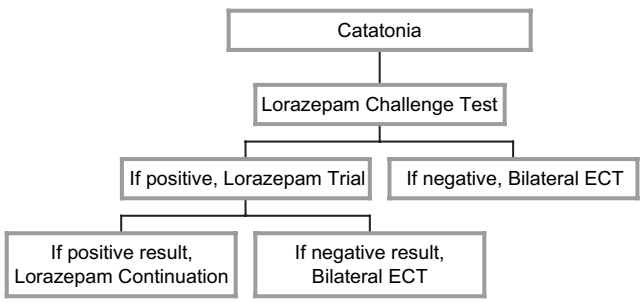

FIGURE 27.10. Algorithm for the medical treatment of catatonia.

Lorazepam treatment in any mode of administration (intravenous, intramuscular, oral) has a wide margin of safety. The most common side effect is sedation that may require special attention in people with chronic obstructive pulmonary disease, obstructive sleep apnea, or obesity. As with any medication, appropriate safe guards should be in place for the occurrence of allergic reactions.

If improvement is seen after the challenge test, treatment with increasing doses of lorazepam as high as 24 mg/day is recommended. Improvement should be observed at least after 3 days before considering bilateral ECT. Once the efficacy of lorazepam is demonstrated, a 6- to 12-month continuation phase commences. Although the usual dose range of 6 to 24 mg/day is considered "high" in conventional psychopharmacology, higher doses are reported to be helpful in catatonia. Lorazepam should be slowly tapered after the continuation phase to avoid withdrawal symptoms caused by tolerance.

ECT is indicated in severe catatonia when the lorazepam challenge test fails or increased dosages do not bring rapid relief. In such circumstances, ECT may be life-saving, and should be promptly considered, even in the face of frequent negative misconceptions regarding ECT in both the professional and lay communities. A few technical issues concerning electrode placement and concurrent medication use need to be considered to maximize the effect of ECT. The efficacy of bilateral (bitemporal or bifrontal) electrode placement is better documented than is unilateral placement, and the use of bilateral placement is, therefore, recommended. All psychiatric medications should be stopped before initiation of ECT, as well as any other nonpsychiatric medications, if possible.

The relief of catatonia often seems to require more frequent seizures than does the relief of major depression. In severe or malignant catatonia, daily treatment for 3 to 5 days may be needed. The number of sessions that will be needed before substantial improvement or remission occurs cannot be predicted. It seems reasonable to assess the patient's overall response after the first 5 or 6 treatments, and then again after 10 or 12 treatments. The cognitive and noncognitive side effects of ECT are well known and manageable (154).

Options for continuation treatment after an effective ECT course may include continuation of the lorazepam treatment or continuation of ECT on an outpatient basis. Although the guidelines for frequency and number of ECT treatments are poorly defined, weekly and biweekly ECT treatments may be needed for up to 6 months to ensure a stabilized response.

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28
Personality Disorders

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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 regarding 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 Character · Contemplation · Meditation · Personality · Personality disorders · Pharmacotherapy · Psychotherapy · Self-awareness · Temperament · Well-being

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 approximately 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 PD.

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 Axis I syndromes.

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 PD diagnosis is 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 raise serious questions regarding the validity and usefulness of categorical personality diagnoses. Fortunately, scientific research allows a clinically practical approach to the assessment and treatment of personality and its disorders that transcends the limitations

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of current official classifications in its usefulness for understanding etiology, development, and treatment (3, 4).

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 their unique adaptations to a changing internal and external environment (5). 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 PD. 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 medications can be helpful adjuncts to therapy (6). 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.

3. What is a Personality Disorder?

The diagnosis of 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 regarding 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 PD 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 of 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 the essential features are learned so that they can be recognized and understood.

3.1. Clinical Features of Personality Disorders

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-IV criteria require that the maladaptive pattern be "of long duration and its onset can

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 teenage years
• Inflexible and pervasive
• Causing subjective distress and/or
• Impaired work and/or social relations
Consistent features
• Strong emotional reactions elicited from others (such as anger or urge to rescue)
• Efforts to blame and change others, rather than oneself
Variable features
• Odd, eccentric
• Erratic, impulsive
• Anxious, fearful

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 PD. 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 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 symptoms 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, DSM-IV categories of PD are symptomatically similar to some Axis I disorders (e.g., paranoid personality and delusional disorder, schizotypal personality and schizophrenia, avoidant personality and social phobia). In fact, most Axis II personality syndromes are treated with interventions proven effective for the corresponding Axis I 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 minutes or more to complete and, as noted above, usually produce multiple diagnoses (5). Consequently, other approaches are needed in practical clinical work (7).

TABLE 28.2. Qualitative clusters and subtypes of personality disorders according to the American Psychiatric Association (DSM-IV, 1994).

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

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4. Deconstructing the Components of Personality and its Disorders

Qualitative terms such as "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, 8). The features that distinguish people with any PD from those with no PD are called character traits. 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 their 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.

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., very resourceful and purposeful and, thus, successful in pursuing their narcissistic or antisocial goals. Their very low cooperativeness (e.g., intolerance of others, low empathy) may so interfere with social relations that they have a PD.

Although 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 (9). 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 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).

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 to attain personal goals, but remains

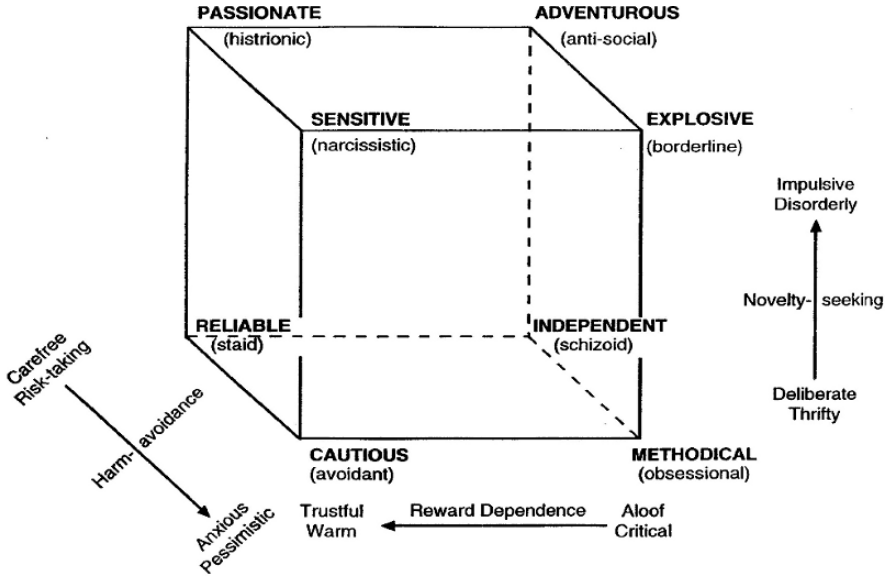

FIGURE 28.1. Discriminating features of most personality disorders shown as the extremes of a cube, with three dimensions defined by novelty seeking, harm avoidance, and reward dependence.

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 their own subconscious thoughts and consider the thought processes of others in a similar way to observing their own thoughts. Hence, the second stage is described as "meta-cognitive" awareness, mindfulness, or "mentalizing." The ability of the mind to observe itself allows for more flexibility in action by reducing dichotomous thinking (10). At this stage, people are able to observe themselves and others for understanding, without judging or blaming. However, in a mindful state, people still experience the emotions that emerge from a dualistic perspective, thus, 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 initial perspective—that is, the preverbal outlook or schemas that direct one's attention and provide the frame that organizes 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 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." The third stage of self-awareness can also be described as "soulful" because, in this state, a person becomes aware of deep preverbal feelings that emerge spontaneously from a unitive perspective, such as hope, compassion, and reverence (4).

TABLE 28.3. Three stages of self-awareness on the path to well-being.

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, therefore, 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").

Adapted from reference (4).

Soulfulness is much more powerful in transforming personality than is mindfulness, which often fails to reduce feelings of hopelessness (11).

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 (12). 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 usefulness 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. I have 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 pp. 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.

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 approximately 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 (13). 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 (14), therefore, 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 such as 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 (i.e., 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.

7. Treatment

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 or parents) are insistent. This usually happens when maladaptive behaviors create marital, family, and career problems, or when other mental symptoms (e.g., anxiety, depression, substance abuse), or somatic symptoms (e.g., obesity), complicate their clinical picture. In general, patients with PD require a multifaceted treatment plan that often combines psychotherapy and pharmacotherapy.

There are three major barriers to effective treatment of PD, but these are preventable errors within the control of the healthcare provider. The first is the frequent loss of professional objectivity, signaled by the development of strong emotions (positive or negative) and called positive or negative countertransference. This inappropriate personal involvement is a red flag to reassess diagnosis and treatment, and often suggests the need for referral to a psychiatrist. Frequent discussions and counseling with colleagues are useful because even strong countertransference feelings sometimes persist unrecognized.

The second preventable error in PD management is to believe the myth that personality disorders cannot be treated effectively. This myth is partly generated by countertransference problems of some professionals, and then sustained by a failure to consider facts showing the effectiveness of treatment. Belief in the untreatability of a patient creates a self-fulfilling prophecy. For example, many controlled studies indicate that even severe personality disorders, such as borderline or antisocial personality disorders, can be effectively treated with an appropriate condition, such as a cooperative therapeutic alliance (15).

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. However, it is most beneficial to provide guidance and support without giving direct advice. All that is usually required in supportive therapy is compassionate attention, respect for the dignity of other human being despite their flaws, and reinforcement of the patient's existing coping mechanisms that are adaptive.

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, usually from personal recognition of 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 their mistakes. In summary, supporting these patients involves joint evaluation of options and encouragement to practice skills in solving problems.

Substantial personality change, which is invariably needed by people with PDs, involves an extensive reorganization of internalized concepts and coping mechanisms and, thus, requires precise diagnostic analyses, 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 their 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 countertransference

reactions), this should help to alert them to the possibility that the patient has a PD.

Because 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 their treatment goals and then jointly evaluate the likelihood of successful outcome until treatment goals that both the patient and the therapist agree on 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," etc.). 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.

7.2. Four Major Stages in Treatment of Personality Disorders

The four stages in the treatment of a patient with PD 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 (16). The initial stage of crisis management and stabilization deals with the presenting problem and stressors 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 (16).

7.2.1. Stabilization Phase

What is done in the first stage of treatment depends greatly on individual patient and their 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 medications 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 nonthreatening 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 toward 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 nonthreatening form of what is usually called cognitive–behavioral therapy and can be safely practiced in a busy office practice with short but regular sessions.

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 of their disorders with the goals of relieving subjective distress and/or conflict with others, thereby preparing them for later stages of treatment that require calmness and nondefensiveness to facilitate growth in self-awareness.

The symptomatic pharmacotherapy of persons with PD focuses on the following four types 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. These four correspond roughly to symptoms most strongly related to the four temperament dimensions. Recommendations regarding drugs of choice in treating PDs are summarized in Table 28.4.

7.2.2.1. 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). Patients with PD often present with both cognitive anxiety (anticipatory worry) and somatic anxiety (concerns about bodily pains and psychophysiological reactions). Cognitive anxiety is most responsive to benzodiazepines and GABA analogs (valproates, lamotrigine), whereas somatic anxiety is more responsive to monoamine oxidase inhibitors (MAOIs), selective serotonin reuptake inhibitors (SSRIs), serotonin–norepinephrine reuptake inhibitors (SNRIs) (e.g., venlafaxine or duloxetine), and buspirone. Low doses of tricyclic antidepressants (TCAs) are very effective for somatic

TABLE 28.4. Choice of drugs according to target symptoms of personality disorders.

Target symptom	Drug of choice	Not recommended
1. Mood dysregulation		
Anxiety		
Chronic cognitive	Serotonergic drugs [a]	
	MAOIs [a]	
	Benzodiazepines	
Chronic somatic	MAOIs [a]	? Benzodiazepines
	SNRIs (duloxetine) [a]	
	Tricyclic antidepressants (TCAs)	
	Beta blockers	
Acute and severe	Low-dose neuroleptics (quetiapine [a])	
Depression		
Atypical depression/dysphoria	MAOIs [a]	? TCAs
	Serotonergic drugs [a]	
	Atypical neuroleptics	
Classic depression	Antidepressants [a]	
Emotional lability	Lithium [a]	? TCAs
	Lamotrigine [a]	
	Olanzapine	
2. Behavior dyscontrol		
Aggression/impulsivity		
Affective aggression ("hot temper" with normal EEG results)	Lithium [a]	? Benzodiazepines
	Serotonergic drugs [a]	
	Anticonvulsants [a]	
	Low-dose neuroleptics	
Predatory aggression (revenge/cruelty)	Atypical [a]	Benzodiazepines [a]
	Neuroleptics [a]	
	Lithium	
Organic-like aggression	Imipramine [a]	
	Catecholamine agonists	
Ictal aggression (abnormal EEG results)	Carbamazepine [a]	Neuroleptics [a]
	Diphenylhydantoin [a]	
	Benzodiazepines	
3. Social dysregulation (asociality)	Atypical neuroleptics [a]	? TCAs [b]
	(Aripiprazole, olanzapine)	MAOIs
4. Cognitive distortion/psychotic symptoms		
Acute and brief psychotic episodes	Atypical neuroleptics [a]	
	Low-dose typical neuroleptics	
Chronic and low-level psychotic-like symptoms	Atypical neuroleptics [a]	
	Low-dose typical neuroleptics	

[a] Drug of choice.
[b] Major contraindication.
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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 low D2 affinity (e.g., quetiapine). Despite the relative safety of novel atypical drugs, caution regarding prolonged use is necessary, as noted above. Emotional instability (manifested as severe mood swings) is usually responsive to lithium (for those with frequent episodes of euphoria) or lamotrigine (for those with more frequent depressive episodes) or with both (for patients with both euphoric and depressive episodes). TCAs, such as imipramine, sometimes increase impulsivity and anger in emotionally unstable patients (e.g., borderline, narcissistic, histrionic, dependent). TCAs are extremely dangerous in an overdose, therefore, 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 response 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, classic depressive episodes, which often complicate PD, are treated with antidepressants, including heterocyclics, in doses suggested for primary major depression.

7.2.2.2. Aggression

It is useful, although sometimes difficult, to distinguish different types of aggression. The most common form of aggression occurs when a quick-tempered person is provoked by frustration or threats. This is often called "affective aggression," and is frequent in impulsive–aggressive individuals (that is, those high in novelty seeking and low in harm avoidance). Aggression that seems to be unprovoked sometimes occurs in patients with cerebral instability documented by an abnormal electroencephalogram (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. In addition, 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 carbonate 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, it 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 decisions to use neuroleptics long-term requires consideration of potential side effects, such as tardive dyskinesia, 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 and catecholamine agonists, 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 SSRIs, and SNRIs that block uptake of both serotonin and norepinephrine) are considered by many to be beneficial for certain impulsive subtypes of PD (e.g., borderline, histrionic). Finally, MAOIs are effective in some dysphoric states with somatic anxiety and hostility, and are also recommended for adult hyperkinetic patients.

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 lying, cheating, and stealing) and it is poorly tolerated by anxious schizoid individuals. 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. The use of benzodiazepines seems appropriate only in non-aggressive behaviors, as are typical of patients with schizoid PD.

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 in which 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, such as 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.

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, psychotic PD patients are likely to respond to and comply with either low doses of powerful neuroleptics or atypical neuroleptics. Because of much better safety and tolerability, new antipsychotics are now the first-choice treatments 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 (illusions), and eccentric behaviors (this is sometimes called "non-psychotic formal thought disorder"). These chronic, low-level, psychotic-like symptoms have been shown to respond to low-dose powerful neuroleptics such as 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, particularly those with a history of drug abuse and suspiciousness. However, long-term use of benzodiazepines is associated with high risk of drug dependence, particularly in patients with PDs, thus, benzodiazepines such as alprazolam should be prescribed only after careful consideration of the risk–benefit ratio and their use should be carefully monitored for evidence of abuse or dependence.

7.3. Second Stages of Personality Transformation

Neither medications nor cognitive–behavioral 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 regarding life. Otherwise, individuals cannot transcend the conflicts among their emotional drives, so they remain in constant or recurrent struggles among parts of themselves.

A systematic approach to personality transformation without tension or conflict is described in more detail elsewhere (4, 16). 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 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

TABLE 28.5. Awakening a positive perspective: transcending problems through spiritual values in life.

Positive approaches to well-being	Experiences and activities	
	Recommended	Not recommended
1. Letting go of struggles	Acts of hope and self-direction. Accepting responsibility. Silence of Mind, phase 1[a] (calm reflection)	Any violence, fighting. Complaining or blaming others. Consumerism feeding greed/addiction
2. Working in the service of others	Acts of kindness/cooperation. Purposeful giving of oneself. Union in Nature.[a] Silence of Mind, phase 2[a] (mindful meditation)	Divisions feeding fear and hate. Possessiveness and hoarding. Seeking power and dominance
3. Growing in awareness	Acts of faith and humility. Transcendent problem-solving. Union in Nature.[a] Listening to the Heart.[a] Silence of Mind, phase 3[a] (contemplation)	Criticism or praise of self and others. Depending on external direction. Denial of what we do not understand
4. Understanding thought processes	Calm reflection. Mindful meditation. Contemplation (Silence of Mind, all 3 phases)	Seeking justification. Depending on external advice. Depending on intellect alone

[a] Meditations for coherence therapy with assessment, treatment, and training information are available for interested clinicians (Cloninger 2004 and http://psychobiology.wustl.edu). The exercises and other useful materials for the awakening phase are a DVD series, The Happy Life: Voyages to Well-Being, available from the non-profit Anthropaideia Foundation at http://aidwellbeing.org. Used with permission of the Center for Well-Being at Washington University.

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 (17). 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 metacognitive 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 (11), 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 nondualistic 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 regarding 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

TABLE 28.6. Physical, personal, social, cognitive, and spiritual therapeutic procedures for advanced character development (Stages 3 and 4 of Coherence Therapy for Personality Disorders).

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 versus rigidity. Nonviolent 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. Reconciliation of approval seeking versus 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. Reconciliation of persistence by virtue. Reflection on mysteries of God, life/death. 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. Practice of Happy Life voyages, Set 1[a]. Practice of Happy Life voyages, Set 2[a]. Practice of Happy Life voyages, Set 3[a].

[a]Treatment and training materials available through http://aidwellbeing.org (4, 16). Used with permission of the Center for Well-Being at Washington University.

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 (18), 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 regarding the treatment of PD is likely to be especially rewarding for both psychiatrists and their patients because it offers a crucial gateway into 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

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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, specific single genes have begun to be identified for disorders such as schizophrenia (e.g., DISC1, neuregulin), bipolar affective disorder (*G72,* BDNF), autism (neuroligins), attention-deficit disorder (DAT, DRD4), AND alcohol dependence (GABRA2, *ADH4*). Genome-wide association studies in large case–control data sets are now in progress, which may confirm and extend such reports. 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 Alcohol dependence · Bipolar affective disorder · Candidate genes · Genetics · Molecular genetics · Schizophrenia · Epigenetics · Endophenotypes

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 and schizophrenia have yielded specific genes. Some of this work has been facilitated by the study of endophenotypes, or biologic vulnerability markers.

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 that is under genetic control should be more "concordant" (similar) in MZ twins compared with 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 with 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.

In adoption studies, the risk for the disorder may be evaluated in four groups of relatives: the adoptive and biological relatives of affected adopted children and the adoptive and biological relatives of control adopted children. If the disorder is heritable, one should find an increased risk among the biological relatives of affected subjects, compared with 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.

1.2. Segregation Analysis

Segregation analysis is used to determine whether the pattern of illness in families is consistent with a specific mode of

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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 into 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 people)

1.3. Linkage Analysis

At any given genetic locus, each individual carries two copies (alleles) of the DNA sequence that 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, whereas 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 is less than 0.5. The probability that the two loci are not linked is the probability that theta = 0.5. Thus, a logarithm of the odds ratio (LOD) score for a family or set of families is defined:

LOD score = $\log_{10}$ [probability of theta less than 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. Because a LOD score is a log value, scores from different families can be summed. For complex conditions, collections of affected sibling pairs may be studied rather than large families. A LOD score of 1.0 indicates that linkage is 10 times more likely than nonlinkage. For simple genetic conditions, a LOD score of 3 or greater is evidence for linkage, whereas 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.

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, whereas 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 disease population compared with 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 (TDT) (3).

1.5. 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 control subjects 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.

1.6. Molecular Genetic Methods

Simple sequence repeat (SSR) markers, also known as microsatellites, represent a group of polymorphisms based on variable numbers of copies of a repeated sequence of two to five nucleotides. The repeated sequence is often ...$(CA)_n$..., ...$(AG)_n$..., or ...$(AAAT)_n$..., although other SSR sequences have been described. The region containing the SSR is amplified by using a thermostable DNA polymerase in a polymerase chain reaction (PCR). Microsatellites are commonly

used to test linkage. A different class of markers, known as single nucleotide polymorphisms (SNPs), are usually used to detect association. SNP detection is now highly automated, permitting thousands of determinations in a single experiment. This is now permitting genome-wide association studies for complex disorders, using gene "chips" with 0.5 to 1 million SNPs embedded on them.

1.7. Gene Expression Studies in Psychiatric Disorders

Identifying genes for psychiatric disorders through classic genetic approaches has proven arduous, despite some recent successes mentioned in this chapter. This is likely because of the 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 (4–6), and is the subject of study of a new field, psychiatric phenomics (7, 8). In addition to heterogeneity, there is also a growing appreciation of the genetic, neurobiological, and phenotypic overlap and interdependence of various major neuropsychiatric disorders (6,9,10). The use of endophenotypes and bootstrapping with other lines of work, neurophysiology (11), imaging (12), and animal models (13), may provide for an accelerated pace of gene identification in the years to come.

The recent completion of the sequencing of the human genome and that of other model organisms, coupled with the advent of microarray technology during the last decade, have made large-scale genomic studies scientifically and economically feasible. After some initial debate about different microarray platforms (14), there is an emerging consensus that different platforms perform with similar accuracy and reliability if used well (15). 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 (16, 17). However, this important line of work, if pursued by itself, suffers from multiple caveats (18)—genetic variability, difficulty of building large enough cohorts, uncertainty regarding exact premortem diagnosis, agonal artifacts (19), impact of comorbid 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 (20).

A combined approach, termed convergent functional genomics, which cross-matches animal model gene expression data with human tissue gene expression data and human genetic linkage/association data, has been developed as a way of avoiding the limitations of the individual approaches mentioned, and reinforcing their strengths in a Bayesian fashion (21). This approach has been applied with some success to bipolar disorder (13, 22, 347), alcoholism (23), and schizophrenia (24). 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 candidate gene association studies and human 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 coexpressed genes (13, 21).

More recently, there has been renewed interest in identifying peripheral correlates of neuropsychiatric disorders, termed biomarkers (347). 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) the diagnosis of illness, 2) early intervention and prevention efforts, as well as 3) the prognosis of the course of the 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 preclinical and clinical (Phase I, II, and III) stages of the process. Lymphocyte protein studies (13) and gene expression profiling (19, 25–28) 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 healthy control subjects, 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, to date, 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 whether 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.

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 of these approaches will provide, in the long term, a sound scientific basis for the development of personalized medicine in psychiatry (29).

2. Epigenetics of Psychiatric Disorders

Epigenetics is the study of heritable biological modifiers of DNA transcription (30, 31). 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, much of which may be captured by the gene expression studies summarized in Section 1.7.

Epigenetic mechanisms have not been demonstrated to be critical in clinical studies of traditional psychiatric disorders to date. Differential methylation does seem 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 chromosomal 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 syndrome, there is deletion of the father's DNA in that region as well, thus, 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. The other model (studied by Frances Champagne at Columbia) 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 seems to also be transmitted to the F2 generation. This is an unusual instance of "inheritance of acquired characteristics," or one example that would seem to support the discredited theories of Lamarck and Lysenko (though this may be mediated by behavior in the F1 animals).

3. Mood Disorders

3.1. Genetic Epidemiologic Studies

3.1.1. Family Studies

Family studies in mood disorder have continually demonstrated aggregation of illness in relatives (32). In a study at the National Institute of Mental Health (NIMH), 25% of relatives of bipolar probands were found to have bipolar or unipolar illness themselves, compared with 20% of relatives of unipolar probands and 7% of relatives of control subjects (33) (Table 29.1). 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 seem 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 disorders into more genetically homogeneous subgroups (34). 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 Section 3.2).

A birth cohort effect has been observed in recent family studies. There is an increasing incidence of mood disorder among persons born more recently. The cohort effect seems to be true for schizoaffective and bipolar illness as well as unipolar illness (35). 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 not known at this time.

TABLE 29.1. Single genes related to bipolar affective disorder—replicated.

Gene	Location	Study (reference)
G72/G30	13q33	Hattori et al., 2003 (46); Chen et al., 2004 (47); Schumacher et al., 2004 (48)
BDNF	11p15	Sklar et al., 2002 (51); Muller et al., 2006 (53)

3.1.2. Twin Studies

Twin studies show consistent evidence for heritability. On the average, MZ twin pairs show concordance 65% of the time and DZ twin pairs, 14% of the time (36).

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 (36).

3.2. The Mood Spectrum (Types of Mood Disorders and Other Disorders that are Genetically Related)

Bipolar I: Classic "manic–depressive illness" with severe mania, generally including episodes of major depression as well.

Bipolar II: Bipolar II disorder is genetically related to bipolar I and unipolar disorder. There is some evidence in family studies for an excess of bipolar II illness in relatives of bipolar II probands (37). It has been demonstrated that bipolar II disorder tends to be a stable lifetime diagnosis (that is, patients do not frequently convert to bipolar I disorder).

Rapid cycling: Rapid-cycling bipolar illness has been the subject of great theoretical and clinical interest. A link with thyroid pathology has been proposed. Rapid cycling seems to arise from factors that are separable from the genetic vulnerability to bipolar illness and that do not lead to aggregation within families. However "rapid switching" of mood, which is related, seems to be familial (38).

Unipolar mania: This entity includes bipolar I patients with no history of major depression. This group is not distinguishable from other bipolar I 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 bipolar disorder (39).

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 (40). These patients 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.

Eating disorders: Family studies of anorexia and bulimia have generally found excess mood disorder in relatives. Relatives of anorexic patients may have similar risk for mood disorders to that of relatives of bipolar probands (36).

Attention-deficit disorder: Children with this disorder seem to have increased depression in their relatives. The opposite has not been demonstrated (bipolar/unipolar probands have not been reported to have increased risk of attention-deficit disorder in their offspring) (37).

Alcohol dependence: There may be overlapping vulnerability traits. Alcoholism seems to be comorbid with unipolar and bipolar disorders (each seems to confer an increased risk for the other within individuals). There is some evidence that alcoholism with mood disorder may itself aggregate within families (41).

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 (43). Recent studies also suggest linkage on 15q25-26 for recurrent early-onset major depression (348).

3.4. Endophenotypes

A number of such markers have been suggested, including:

- REM sleep induction by cholinergic drugs
- White matter hyperintensities on magnetic resonance imaging (MRI)
- Amygdala activation on functional MRI (fMRI)
- Hippocampal size
- Response to tryptophan depletion
- Response to sleep deprivation

See the review in Hasler et al. (43) for additional information.

3.5. Gene Expression Studies

See Ogden et al. (44) for information

3.6. High-Risk Studies

More offspring of patients than control subjects have a diagnosed Axis I disorder. Offspring of bipolar parents may be more prone to respond to dysphoric feeling states by "disinhibitory" behavior (45).

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– 29.3). We feature these genes here.

TABLE 29.2. Single genes related to bipolar affective disorder—meta-analysis.

Gene	Location	Study (reference)
5HTT	17q	Cho et al., 2005 (54)
MAO-A	X	Preisig et al., 2000 (55)

TABLE 29.3. Single genes related to bipolar affective disorder—single studies.

Gene	Location	Study (reference)
DISC1	1q42	Millar et al., 2000 (56); Thomson et al., 2005 (57)
P2RX7	12q23-24	Barden et al., 2006 (58)
GRK3	22q11	Barrett et al., 2003 (59)

G72 (46–48): This gene is one of two implicated together in association studies on chromosome 13q. The gene G30 is a DNA sequence that is reverse transcribed within G72. The association was first identified by Hattori et al. (46) 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. (49), shows association not only with bipolar illness, but with a subset of subjects with schizophrenia who also had clear mood episodes. The function of G72, sometimes referred to as DAOA (d-amino acid oxidase activator) may be 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. However we should note that recent studies by Kvajo et al., (349) support a role for G72 in neuronal morphology but not in glutamate signaling.

Brain-derived neurotrophic factor (BDNF) (30,31,50–53): 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) (56, 57): 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 seems to interact with phosphodiesterase 4B, which may play a role in mood regulation.

5HTT and MAOA (10, 54, 55): These two genes have been shown in meta-analyses to be associated with bipolar disorder, even though no strong effects were shown in any one study. The effect size for each seems to be in the range of 10 to 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 [AP], and schizophrenia, respectively).

P2RX7 (aka P2X7, P2X7R) (58): This gene on 12q24 was identified in a French–Canadian case–control series in linkage studies using large pedigrees from the same population. It is a calcium-stimulated ATPase. The data are suggestive, but await replication in an independent study.

GRK3 (59): The only candidate identified using animal model studies (a mouse model using 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 downregulation of G protein-coupled receptors.

3.8. Empirical Data for Genetic Counseling

Molecular genetic studies hold great promise in the future for families with Mood disorder, particularly bipolar disorder. However, genetic counseling currently is based on empirical risk figures.

The lifetime risk for severe (incapacitating) Mood disorder is approximately 7%. Risk is increased to approximately 20% in first-degree relatives of unipolar patients, and 25% in first-degree relatives of bipolar patients. Risk seems to be 40% in relatives of schizoaffective patients. The risk to offspring of two affected parents is in excess of 50% (Fig. 29.1 and Color Plate 7, following p. 650; Tables 29.4 and 29.5). Overall risk

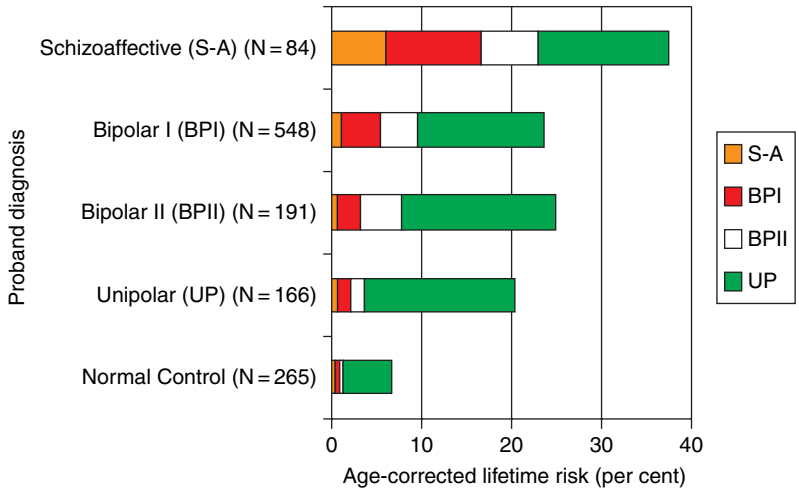

FIGURE 29.1. Age-corrected lifetime risk for relatives of subjects with schizoaffective disorder (S-A), bipolar disorder I (BPI), bipolar disorder II (BPII), unipolar disorder (UP) and healthy control subjects for developing the disorders listed above (*see* Color Plate 7, following p. 650).

TABLE 29.4. Lifetime risk for severe major affective disorders in different groups.

General population	7%
Relatives of UP	20%
Relative of BP	25%
Relatives of SA (BP)	40%
Children of two ill parents	50%+
Identical twin ill	60%

TABLE 29.5. Lifetime risk for bipolar disorder in different groups.

Control subjects	0.5–1%
Relatives of UP	3%
Relatives of BP	8%
Relatives of SA	17%
MZ twin	80%

figures seem to be rising in recent years, but more so in relatives of patients than in the general population (keeping at approximately a 3:1 ratio). Average age of onset is approximately 20 years of age for bipolar disorder and 25 years of age for unipolar disorder.

4. Alcoholism

4.1. Epidemiologic Genetic Studies

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. (60, 61). 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., ~39% of the variance between members of a twin pair is caused by genetic factors) for frequency of drinking and 0.36 for amount consumed per session. A second Finnish study by Kaprio et al. (62) included data on several thousand pairs of twins in the state twin registry. Overall heritability for total alcohol consumption was 0.37 in men and 0.25 in women. Clifford et al. (63) report a study in which 572 twin families from the Institute of Psychiatry register were examined (including a total of 1,742 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 men.

Twin studies of alcoholism itself have generally shown heritability. Kaij (64) studied registration of twin subjects at the Swedish County Temperance Boards. Such registration implies that a complaint was made regarding a person's behavior while drinking, either by the police or a third party. This would not generally include alcoholic individuals who were socially isolated, although 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, proband-wise concordance was 54.2% in MZ twins and 31.5% in DZ twins ($P < 0.01$). Concordance rates in MZ twins increased with the severity of the disturbance. A reanalysis of these data by Gottesman and Carey (65) shows heritability to vary from 0.42 to 0.98, with the more serious forms of alcoholism being more heritable.

Kendler et al. (66) conducted a population-based study of female twin pairs from the Virginia twin registry. Personal interviews were completed on 1,033 of 1,176 pairs. MZ concordance varied from 26 to 47% (narrow to broad definition of alcoholism) whereas DZ concordance ranged from 12 to 32%. Calculated heritability was 50 to 61%. This

suggests substantial genetic influence in alcoholism in women in the populations studied.

4.1.2. Adoption Studies

Goodwin et al. (67) compared 55 adopted-away male children of an alcoholic parent with 78 adopted children 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 individuals compared with 5% of the control subjects ($P < 0.02$). Goodwin also compared adopted-away sons of alcoholic individuals with sons of alcoholic individuals raised by the alcoholic parent (68). There was no difference.

Bohman (69) used state registers in Stockholm to study 2,324 adoptees born in Stockholm 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% versus 13.6%; $P < 0.01$) compared with adoptees without an alcoholic (or sociopathic) father. Cloninger, Bohman, and Sigvardsson (70) then reanalyzed Bohman's data set, and postulated a familial distinction of alcoholic individuals: the milieu-limited (type I) and male-limited (type II) groups. Type I alcoholic individuals (as defined in Cloninger (71)) usually have onset after age 25 years, manifest problems with loss of control, and have a great deal of guilt and fear regarding alcohol use. Type II alcoholic individuals have onset before age 25 years, are unable to abstain from alcohol, and have fights and arrests when drinking, but less frequently show loss of control and guilt and fear regarding alcohol use. Cloninger reanalyzed the Stockholm Adoption data using these specific categories. This analysis showed that type I alcoholic individuals 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 control subjects with no risk factors. Type II alcoholism was present in only 1.9% of the control subjects, but 16.9 to 17.9% of adoptees with genetic risk factors, whereas the presence or absence of environmental risk factors (alcoholism in adoptive parents) did not seem to make a difference.

Bohman et al. (72) extend this finding to female adoptees, identifying as particularly important the incidence of alcoholism in the biologic mothers of these adoptees.

4.1.3. Family Studies

Family studies of alcoholism have been reviewed by Cotton (73) and Goodwin (74). Both reviews concluded that there is a concentration of alcoholic individuals in the families of alcoholic probands. Cotton (summarizing 39 studies on families of 6,251 alcoholic individuals and 4,083 nonalcoholic individuals) reports an overall prevalence of 27.0% alcoholism in fathers of alcoholic individuals and of 4.9% in mothers; 30.8% of alcoholic individuals 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 control subjects reviewed in the same study show a rate of 5.2% in fathers and 1.2% in mothers. Nurnberger et al. (75) 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 alcohol abuse according to the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (DSM-IV) does not arise from the same genetic factors as DSM-IV alcohol dependence.

4.2. Disorders Genetically Related To Alcoholism

Winokur et al. (76) reported an increased prevalence of depression in the female relatives of alcoholic individuals 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. (72) and Cloninger et al. (77) have observed that adopted-away daughters of type II (male-limited) alcoholic individuals 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 alcoholic individuals may transmit both alcoholism and sociopathy as part of the same syndrome.

Earls et al. (78) 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. (79) report that drug abuse in adoptees is associated with alcohol problems in first-degree biologic relatives.

Nurnberger et al. (75) found substance dependence, several anxiety disorders, and major depression increased in the relatives of probands with alcohol dependence.

4.3. Linkage Studies

Several linkage studies have been completed in sizeable populations. Genes predisposing to alcohol dependence seem to be located on chromosomes 1, 2, 4, 7, and 16 (80, 81).

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 electroencephalogram (EEG) (which are inversely related to inhibitory neuronal activity in the cortex) and to alcohol dependence (82). The association with alcohol dependence has now been replicated by four other groups. This gene seems to be particularly strongly related to vulnerability to problems with impulse control, because the risk allele is seen in adolescents with conduct disorder and in those alcohol-dependent people who also have drug dependence (83). Other GABA receptor genes, such as GABRG3, may also be associated with alcohol dependence (84).

ADH4: Alcohol dehydrogenase (ADH) 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, SNPs in some of the ADH enzymes (genes for several isoenzymes of ADH are located on chromosome 4q) have been associated with alcohol dependence in white populations and in Native Americans. The strongest finding is in ADH4 (85), and this seems to be associated with early onset of regular drinking (unpublished data).

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 (86). 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 (87)).

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 (88).

DRD2: Originally reported approximately a decade ago, the literature on DRD2 is still controversial. A meta-analysis of 21 studies shows an increased risk of 50 to 100% for persons carrying the A1 allele (89). However, recent work has questioned whether this polymorphism may actually be reflecting variation in a gene next to DRD2 (350).

4.5. 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 ingestion, 3) psychologic/psychophysiologic differences, and 4) behavioral and neuroendocrine responses to alcohol.

Alcohol is primarily metabolized in the liver by the enzymes ADH and 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 (90). The ALDH2 enzyme is lacking in approximately 50% of Japanese subjects tested (91) and apparently in other Asian 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 control subjects (92–95). Major et al. (95) report reduced MAO activity in liver but not brain samples from chronic alcoholic individuals. Perhaps most interesting is the report from von Knorring et al (96), suggesting that low MAO is related only to type II alcoholism. Confirmatory evidence was reported by Sullivan et al. (97).

A poorly synchronized resting EEG (lower alpha rhythm) has been thought to be related to a predisposition for alcoholism (98). Change in alpha rhythm after alcohol ingestion is more concordant in MZ than DZ twins (as are multiple other EEG parameters) (99, 100). A relationship was found between resting EEG of the unselected twins and drinking behavior (less alpha rhythm in the twins who drank more). In subsequent work, Propping et al. (101) found that relatives of alcoholic individuals with poorly synchronized resting EEGs demonstrated the same characteristic themselves. Change in alpha rhythm after alcohol consumption was also found to differentiate young adult subjects at high risk for alcoholism from control subjects (102).

Measurements of event-related potentials have shown smaller P300 waves after visual stimuli in 7 to 13 year old sons of alcoholic individuals compared with control subjects (103), lessening the likelihood of previous alcohol exposure. Similar findings using an auditory stimulus had been reported in an older group (age 21–26 years) both before and after alcohol administration (104). Hill et al. (105) found a significant increase in P300 latency in adolescent and adult relatives of alcoholic individuals compared with control subjects. The EEG/ERP (event-related potential) 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 alcoholic individuals displayed less subjective intoxication than control subjects (106–108). A follow-up study by Schuckit (109) shows that decreased

subjective intoxication is correlated with later development of alcoholism in sons of alcoholic individuals.

4.6. Summary

There seem 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, although even here the interaction between genotype and environment in different ethnic groups may result in very different outcomes (110). 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 sex 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 inheritance) and type II (or male-limited inheritance). 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 seem to operate by independent pathways. GABRA2 alleles seem 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 (111).

5. Alzheimer's Disease

Genetic etiologies for some forms of Alzheimer's disease (AD) 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 genetic. 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.

5.1. Twin Studies

A total of 81 twin pairs, in which at least one member is affected with 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.

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 (112) 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 years, compared with 7% for relatives of control subjects (demented subjects without agraphia).

There are divergent opinions concerning the degree to which AD is familial, depending on 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.

5.3. Linkage Studies

In 1987, St. George-Hyslop et al. (113), reported linkage of familial AD to restriction fragment length polymorphism (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 (114, 115). 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 AD is a gene on chromosome 14 (116). Additional families are linked to a gene on chromosome 1. The genes on chromosome 1 and 14 code for proteins named presenilins and seem to be highly homologous.

Many late onset families may show linkage to a region of chromosome 19 coding for lipoprotein E (usually abbreviated as ApoE), which is also implicated in cardiovascular illness. One copy of the E4 allele will increase risk fourfold compared with those with E2 alleles. Two copies of E4 increase risk by a factor of eight. ApoE does not seem to be a strong risk factor in African populations, although it is in African American populations (117). Differences may be related to diet and other environmental factors associated with lipid metabolism and vascular damage. The molecular mechanisms for the AD vulnerability genes are now the subject of intense investigation. There is reason to suspect that they all may have an effect on accumulation of amyloid.

6. Antisocial Personality Disorder

6.1. Epidemiologic Studies—Twin Studies

In a Danish twin study 32.6% (28 of 86 pairs) of MZ twins were concordant for criminal behavior, compared with 13.8% (21 of 152 pairs) of DZ twins ($P < 0.001$). In a Norwegian twin study, Dalgard and Kringlen (118) found a higher MZ concordance (8 [25.8%] of 31 pairs) for crime compared with the DZ concordance (8 [14.8%] of 54 pairs), but this failed to reach statistical significance ($P = 0.11$).

Schulsinger (119) and Crowe (120) 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 of 46 adoptees of female felons met criteria for AP compared with 0 of 46 control adoptees (120). 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 12 (3.9%) of 305 biological relatives of AP adoptees, compared with 4 (1.4%) of 285 biological relatives of control adoptees, a highly significant difference. If only the fathers were considered, 5 (9.3%) of 54 probands' biological fathers received a diagnosis of AP compared with 1.8% of the biological fathers of control adoptees. In a larger study, using adoption and criminal registries, Mednick et al. (121) reported that when neither the biologic nor the 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 Cloninger et al. (122). They reported that both genetic and "postnatal" influences were detectable in the risk for AP. When postnatal factors predisposed to criminality, 8 (6.7%) of 120 male adoptees were criminal compared with 19 (2.9%) of 666 male adoptees with nonpredisposing postnatal and genetic backgrounds. When the genetic background, but not the postnatal environment, was predisposing, 12.1% of male adoptees were criminal compared with 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).

6.2. Epidemiologic Studies—Family Studies

Of 223 male criminals, 80% were found to have a diagnosis of AP (123). Sixteen percent of the interviewed male first-degree relatives also had this diagnosis, whereas only 2% of female relatives had AP, compared with 3% and 1% in the relatives of control subjects. 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 (124). Predictably, the male relatives had a threefold increase in AP (31%) compared with the female relatives (11%). The increased risk for AP among first-degree relatives of female felons (31%) compared with the risk for relatives of male felons (16%) may be related to a greater genetic and social predisposition that may be present in the families of the female felons, yielding a higher risk in these relatives.

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 in 1,000 male newborn infants, but Hook found XYY in 1/53 from 3,813 males in 20 penal/mental institutions. Witkin et al. (125) surveyed all tall Danish men from a birth cohort, finding 12 (0.29%) of 4,139 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.

6.4. Biological Markers

Nielsen (126) 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 and with suicide attempts in violent criminal offenders. Goldman has reported a replication of this finding. 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 (127). Low 5HIAA level has been associated with impulsivity and violence in experimental colonies of rhesus monkeys (128, 129) as well as in humans (130, 131). A Dutch family was reported with lowered MAOA activity caused by a point mutation on the eighth exon of the MAOA gene. The men with this mutation (both MAO genes are on the X chromosome) showed impulsive aggression, arson, attempted rape, and exhibitionism (132). It seems likely that other familial monoamine defects may be found to be associated with aggressive behavior.

7. Anxiety Disorders

Observations on the increased familial risk for anxiety disorders have been recorded in the literature for longer than 100 years. Family studies of panic disorder 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 with relatives of control subjects (133). There was also a fivefold 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 with 1.9% for relatives of panic probands and 1.5% for control probands. A study of simple phobia (134) found an increased risk (31%) for simple phobia among relatives of probands with that diagnosis (but no other anxiety disorder) compared with relatives of well probands (11%). A family history study of social phobia (135) demonstrated that relatives of phobic probands were at increased risk for this disorder (6.6%) compared with relatives of panic disorder probands (0.4%) or relatives of control subjects (2.2%).

Distinctly separate genetic transmission for generalized anxiety disorder is not well established. In a family study, Noyes et al. (136) found that relatives of probands had a greater risk than relatives of control subjects, 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, although 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.

7.1. Twin Studies

In a Norwegian sample (137), the concordance of all anxiety disorders for MZ twins (34.4%) was significantly greater than that for DZ twins (17.0%).

7.2. Linkage Studies

Crowe has studied 26 families with multiple cases of panic disorder, including 198 informative persons, 39% of whom have definite or probably panic disorder (138). Hamilton and colleagues (139) reported a syndrome linked to chromosome 13q; the complex phenotype included anxiety disorders and urinary tract dysfunction.

8. Attention-Deficit Disorder

Early family studies of attention-deficit disorder noted alcoholism and sociopathy in male relatives and hysteria in female relatives (140). This same constellation was not manifest in the adoptive parents of adopted children with attention-deficit disorder (141).

Family studies suggest that antisocial personality aggregates in the relatives of children with attention-deficit disorder, specifically when the probands have had conduct or oppositional disorder (142). Biederman and colleagues found rates of mood illness increased in relatives of their group as well. Attention-deficit disorder itself was also increased in relatives, and attention-deficit disorder and antisocial behavior tended to occur together.

Hauser et al. (143) reported mutations in the gene for the thyroid hormone receptor in one group of subjects with attention-deficit disorder (143). A family-based association study has implicated a gene for the dopamine transporter (144). The gene coding for the DRD4 receptor has been associated with attention-deficit hyperactivity disorder in a meta-analysis (145). Genetic results have stimulated extensive investigations on the pathophysiology of attention-deficit disorder in recent years, particularly related to the dopamine neurotransmission system.

9. Autism (Pervasive Developmental Disorder)

The pooled frequency of autism in siblings is approximately 3% (146), which is 50 to 100 times the population rate. Folstein and Rutter (147) 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, although carefully selected, was small (n = 21), but the essential conclusions regarding heritability have been borne out in studies by Le Couteur et al. (148) and Steffenburg et al. (149).

A segregation analysis in a series of multiplex families was consistent with autosomal recessive inheritance, although the excess of affected male subjects in the sample suggests sex-specific modifying factors (150). What is perhaps more striking regarding the known genetics of autism is the association of multiple single-gene disorders with the syndrome. The most clearly documented of these disorders is Fragile X syndrome; perhaps 8% of autistic subjects have the cytogenetic Fragile X and 16% of Fragile X male subjects are autistic (151). However, studies in a series of families did not provide evidence for a major role of Fragile X mutations in autism (152). 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 has been summarized by Reiss et al. (153). 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 in which both twins have a narrowly defined phenotype of autism or where one sibling 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 (154) (IMGSAC) (155–157). This region has been

designated AUTS1 and stretches from genetic marker D7S524 (104.86 cM) to D7S483 (176.48 cM). The highest nonparametric multipoint MLS score achieved in one analysis was 3.2 at D7S477 (119.6 cM) (157); and a LOD of 3.6 at D7S530 (145 cM) was seen in another study (153). Folstein (158) 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 (maximum likelihood score) of 3.74 (156). This region is weakly supported by an earlier study by Philippe et al. (159). 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 prenatal and early postnatal murine brain development.

Because of 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 (160, 161). Candidate gene studies have implicated the serotonin transporter, reelin, and the neuroligins as possible single genes associated with the autism spectrum.

10. Drug Abuse

Cadoret et al. (79) reports an adoption study of drug abuse. Four hundred forty-three 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 drug abuse in the absence of antisocial behavior. Environmental factors implicated included divorce and significant psychiatric pathology in the adoptive parents.

Grove et al. (162) report a study from the Minnesota sample of 32 MZ twins raised apart. Significant heritability was shown for drug abuse or dependence. The proband-wise concordance was 36%. Concordance in this range suggests a combination of genetic and environmental effects.

Mirin et al. (163) 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. (164) reported significantly increased risk for substance abuse, alcoholism, antisocial personality, and major depression among the relatives of opiate-dependent probands compared with control subjects.

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 (165). In humans, variants in the mu receptor gene do not seem to be associated with opiate dependence but are associated with response to naltrexone among alcohol-dependent patients (166) and with response to nicotine replacement therapy among smokers (167). The National Institute on Drug Abuse (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. Results are still being analyzed, but preliminary presentations suggest that important single gene variations will be uncovered with this technique (168).

11. Eating Disorders

11.1. Family Studies

Controlled family studies on eating disorders have been conducted during the past two decades. These studies suggest that there is considerable familial aggregation. Table 29.6 summarizes the results from these studies. It is difficult to estimate precisely the risk to first-degree relatives because the control samples are not sufficiently large to detect more than one to two affected relatives of control subjects. However, the overall pattern suggests substantial risk, almost certainly greater than relative risk (RR) equal to 10, and perhaps much larger. There are increased rates of anorexia nervosa among first-degree relatives of probands, and increased rates of bulimia nervosa among first-degree relatives of anorexia nervosa probands. This clustering of eating disorders in families of anorexia nervosa and bulimia nervosa individuals provides strong support for familial transmission of both disorders.

11.2. Twin Studies

There have been a number of twin studies of anorexia nervosa. However, many of the studies were small and often had methodological weaknesses. If one examines the twin studies with the largest number of subjects and most appropriate

TABLE 29.6. Risk for anorexia nervosa.

Study (reference)	Risk for anorexia nervosa among first-degree relatives of anorexia nervosa probands	Risk for anorexia nervosa among first-degree relatives of control women
Gershon, 1983 (169)	2.0% (n = 99 relatives)	0% (n = 265 relatives)
Logue, 1989 (170)	1.3% (n = 153 relatives)	0% (n = 103 relatives)
Strober, 1990 (171)	4.1% (n = 387 relatives)	0% (n = 703 relatives)
Herpertz-Dahlmann, 1988 (172)	4.3% (n = 69 relatives)	0% (n = 69 relatives)
Lilenfeld, 1998 (173)	1.1% (n = 93 relatives)	0% (n = 190 relatives
Strober, 2001 (174)	3.4% (n = 290 relatives)	0.3% (n = 318 relatives)
Mean	3.1% (34/1,091 relatives)	0.06% (1/1,648 relatives)

methodology (175, 176), 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. Studies that are more recent 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. These studies are summarized in Table 29.7.

Holland et al. (175) report pair-wise concordance of 56% in MZ and 5% in DZ pairs (71% and 10% with proband-wise 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 co-twins 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 to 76% of the variance in the liability to anorexia nervosa (178), and 54 to 83% of the variance in the liability to bulimia nervosa (183, 184) 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 (185). For both anorexia nervosa and bulimia nervosa, the remaining variance in liability seems to be caused by 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 seem to be moderately heritable. Twin studies of binge eating, self-induced vomiting, and dietary restraint suggest that these behaviors are roughly 46 to 72% heritable (186, 187). Likewise, pathological attitudes such as body dissatisfaction, eating and weight concerns, and weight preoccupation show heritabilities of roughly 32 to 72% (181, 187–189). Taken together, findings suggest a significant genetic component to anorexia nervosa and bulimia nervosa as well as the attitudes and behaviors that contribute to, and correlate with, clinical eating pathology.

11.3. Molecular Studies

The first anorexia nervosa linkage scan was based on approximately 200 multiplex kindreds and revealed a locus on 1p (NPL (non-parametric LOD) score = 3.5 at D1S3721; 72.6 cM) (190). Additional genotyping in the region resulted in an increased NPL score of 3.91 at 72.0 cM (191). Analysis of diagnostic phenotypes, using obsession scale scores and drive for thinness scores as covariates, revealed additional linkage peaks (192). SNP genotyping at several candidate genes (5ht1dr, hcrtr1, and oprd1) revealed limited evidence for association with the 5ht1dr and oprd1 genes. These observations were confirmed in an independent population of anorexia nervosa individuals (193).

The first bulimia nervosa linkage scan was based on approximately 300 multiplex families and yielded a genome-wide significant LOD score of 2.92 on chromosome 10p. When analysis was restricted to those approximately 133 multiplex kindreds characterized by self-induced vomiting, the LOD score on 10p increased to 3.39. A promising candidate gene within the 10p linkage peak is glutamic acid decarboxylase 2 (GAD2), a gene implicated in obesity (194).

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 (183). More recently, larger samples sizes have been used in candidate gene studies, using collaborative, multisite approaches.

TABLE 29.7. Twin studies of anorexia nervosa.

Study (reference)	Country	Additive genetic (95% CI)	Family environment (95% CI)	Residual (95% CI)
Wade et al., 2000 (178)	USA	0.58 (0.33–0.84)	0	0.42 (0.16–0.68)
Klump et al., 2001 (179)	USA	0.76 (0.35–0.95)	0	0.24 (0.05–0.65)
Kortegaard et al., 2001 (351)	Denmark	0.48 (0.28–0.65)	0	0.52
Bulik et al., 2006 (182)	Sweden	0.56 (0–0.87)	0.05 (0–0.64)	0.38 (0.13–0.84)

CI, confidence interval.

For example, Ribases (195) reported that the Met allele of a missense variation in the BDNF gene was associated with anorexia nervosa in Spanish patients. Subsequently, this was confirmed (196, 197) in European collaborative samples totaling greater than 1,500 patients.

12. Mental Retardation

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 retarded child has been estimated to range from 9.5 to 23%, depending on the severity of the disorder and the mother's reproductive history (198). For mothers who have already had more than one retarded child, the risk is 25 to 50% for siblings.

12.2. Specific Etiologic Causes

Many medical syndromes are manifest as mental retardation, such as specific errors of metabolism and chromosomal anomalies (199, 200). Polani (201) estimates that 4% of human conceptions are chromosomally abnormal, but that 85 to 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 mental retardation, Koranyi lists five dominant diseases (tuberous sclerosis, neurofibromatosis, Sturge-Weber disease, von Hippel-Lindau, 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 Mendelian Inheritance in Man (MIM http://www.ncbi.nlm.nih.gov/sites/entrez?db=omim).

If we consider disorders causing mental retardation according to their frequency in the population, we may see the following. Down's syndrome accounts for mental retardation in 1.5 persons per 1,000 and is the most common single cause of the condition (202). The prevalence of Down's syndrome varies greatly and is primarily determined by maternal age. Familial microcephaly is present in approximately 1 in 40,000 births but may account for a significant proportion of mental retardation because of effects in heterozygotes. Fragile X syndrome is present in approximately 0.5 in 1,000 births and other X chromosome syndromes in another 1 in 1,000 births. All metabolic causes together are responsible for 1 in 1,000 births and chromosomal abnormalities for 3 in 1,000 births.

12.2.1. Down's Syndrome

Down's syndrome is well studied and 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 (203, 204). It is probable that sections of 21q22.2 and 21q22.3 are involved, although some work implicates 21q21 (205). The areas implicated include genes for amyloid and superoxide dismutase. The ETS-2 proto-oncogene is also near this area, and its presence may be related to the well-described increased incidence of leukemia in persons with Down's syndrome and their relatives (206–208). Human 21q21-22.3 is homologous to portions of mouse chromosome 16. A mouse model of Down's syndrome has been described based on a laboratory-generated reciprocal translocation involving this area (209, 210).

The reasons for triplication or nondisjunction in Down's syndrome 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 syndrome patients have a translocation rather than a triplication (211).

As noted above, the clearest correlate is maternal age. However, it has been known for some years that the origin of the nondisjunction may be paternal as well as maternal (212). 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 (213).

It has been reported (208) that a familial association exists between AD and Down's syndrome, but this is unlikely to be generally true (214). 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 (215).

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 (216). The Fragile X (breakage at Xq27.3) is merely the best known. The syndrome itself was originally described by Martin and Bell (217), who described a large pedigree with mental retardation segregating in an X-linked recessive pattern.

Fragile X is the most common form of X-linked mental retardation and is, in general, the most common heritable form of mental retardation (Down's syndrome being genetic but not inherited). It is estimated that 1 in 850 persons carry the defect. Of those, four of five male individuals will express the clinical phenotype as compared with one of three female individuals (thus, some homozygotes are nonpenetrant and some heterozygotes are penetrant). Tests are now available to determine carrier status in nonpenetrant individuals; the error rate

should now be 5% or less with available probes, and new polymorphisms are being developed at a rapid rate (218,219). 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 mental retardation. However, Reiss et al. (220) have demonstrated schizotypal features in approximately one third 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 (152, 221). Mendlewicz and Hirsch (222) described a family in which Fragile X syndrome segregated with manic depressive illness and in which 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 (223). Raymond and Tarpey (224) have reviewed the general area of genetic causes of mental retardation.

13. Obsessive–Compulsive Disorder

13.1. Epidemiologic Research—Twin Studies

There are no large twin studies of obsessive–compulsive disorder (OCD). Rasmussen and Tsuang (225) reviewed reported series and noted that 32 (63%) of 51 MZ pairs were concordant. However, assignment of diagnosis and zygosity has been questioned in some of these cases (226). 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. (227) studied 145 first-degree relatives of 46 children with OCD. Of the 90 parents personally evaluated, 15 (17%) received a diagnosis of OCD, compared with 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% (228). Fathers were three 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.

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 is 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 gene associated with OCD in a single pedigree (229).

14. Schizophrenia

14.1. Twin Studies

Twin studies of schizophrenia were summarized by Nurnberger et al. (230). Several conclusions were drawn from these data. First, MZ twin concordance is greater than DZ 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. (231) 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 (232) and investigations of viral etiology (233, 234).

Inouye (235) reported on a series of nine MZ twins with schizophrenia who were raised apart from infancy. Three were regarded as completely concordant and three were partially concordant.

Abe (236) used 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 2 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, whereas twins living apart do not. This is an intriguing finding suggesting an environmental factor.

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 (237). 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 to 4%.

Thus, close relatives of schizophrenic patients suffer approximately 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 seems to develop "spectrum" disorders (see Sect. 14.4). However, the majority of close relatives of schizophrenic patients are psychiatrically healthy.

It is hard to make a strong case for genetic determination of the classic subtypes of schizophrenia (Kraepelin's hebephrenic, catatonic, and paranoid forms). Although there is significant concordance in MZ twins for subtype (237), this does not hold true in family studies (238).

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 control subjects, Gershon et al. (40) 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 (239, 240).

14.3. Adoption Studies

The adoption study methodology was first applied to schizophrenia by Heston (241), who found more schizophrenia in the adopted-away offspring of schizophrenic women than in control adoptees. A series of large, systematic studies were carried out by Kety et al. (242–244) and Rosenthal et al. (245), 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 nonrelatives. 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 healthy adoptees. The prevalences of psychiatric illnesses in the adoptive relatives of the two groups were small and comparable.

Rosenthal et al. (245) also found the frequency of schizophrenia spectrum disorders to be higher in adopted-away offspring of schizophrenic parents than in the adopted-way offspring of healthy parents. All of these studies have been criticized for the selection of subjects, validity of diagnoses, and validity of comparisons (246, 247). However, further independent analysis of the data has confirmed the essential results: that is, biologic relatives of schizophrenic patients 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 (248, 249).

14.4. Spectrum

Several investigations in this area have been performed by Baron and coworkers (250). 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. (251) have argued that the evidence for schizotypal personality disorder being part of the schizophrenia spectrum is strong, with suggestive evidence for paranoid and schizoid disorder as well. Kendler (252–254) has argued for a separate entity characterized by paranoid delusions only (simple delusional disorder), with inheritance independent of schizophrenia and mood disorders.

14.5. Molecular Studies

Multiple linkage scans of the genome have been conducted with a diagnostic phenotype of schizophrenia, using DSM-IIIR, DSM-IV, ICD, and/or Research Diagnostic Criteria. These linkage scans have been the subject of meta-analyses (255, 256) 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 are discussed next, with a focus on those with highly promising candidate genes.

On chromosome 6p, Straub et al. (257) first published evidence that the dysbindin (DTNBP1) gene showed association with schizophrenia. Multiple confirmations followed (259–262), although some negative reports exist (263). Multiple haplotypes have been associated with schizophrenia in these reports. There is evidence that dysbindin levels are reduced in postmortem schizophrenia brains (264–266). A SNP in the 3'-untranslated region (UTR) of the dysbindin gene may mediate the reduced expression (265, 266). At least one dysbindin risk haplotype may be associated with decreased cognitive ability (267). There may be some overlap between psychotic bipolar disorder and schizophrenia in terms of dysbindin risk alleles (268).

An 8p candidate gene, neuregulin 1 (NRG1), was associated with schizophrenia (269–276). Although there is substantial genetic evidence for a NRG1 role in the genetics of schizophrenia, other investigators (some using multiplex samples with positive linkage signals in the region) could not confirm the NRG1 association with schizophrenia (277–282). Interestingly, Green et al. (283) found evidence for association of NRG1 alleles with psychotic bipolar disorder, suggesting some genetic overlap between this entity and schizophrenia.

Chumakov et al. (284) 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 messenger RNA (mRNA) in postmortem human brain tissue. 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 was renamed DAO activator (DAOA) though see (349). Associations between DAOA and schizophrenia have been reported in samples from China (285), Germany (286), Ashkenazis (287), South Africa, and the United States (288). Childhood-onset schizophrenia has also been associated with DAOA in a small sample (289). Various risk alleles and haplotypes have been reported in schizophrenia. Curiously, multiple independent data sets suggest that this locus contributes to risk for bipolar disorder (46, 47, 47–49). No clear functional variation has been found.

Several other candidate genes have been implicated repeatedly in the etiology of schizophrenia, including RGS4 (289), COMT (290, 291), and DISC1 (56).

14.6. Endophenotypes in Schizophrenia

The concept of endophenotypes in psychiatric disorders has been developed during the last several decades. Gottesman and Shields (292) 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 with the entire spectrum of disorders included in the nosologic category.

The usefulness 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 that 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, molecular level can be made.

14.6.1. Criteria for an Endophenotype

Criteria for an endophenotype have been derived from those proposed by Gershon and Goldin (293):

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 with the general population

Below, examples of promising endophenotypes in schizophrenia are summarized.

There are many reports of attentional deficit measures in schizophrenia. An endophenotype that 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 (294). The fraction of individuals with schizophrenia who are designated as having abnormal working memory varies with the tests used, the clinical population studied, and the definition of abnormal (e.g., 1.5 or 2 standard deviation units below the mean for control subjects). If consideration is given only to studies of large numbers of cases ($\sim$100 cases) and control subjects, most reports describe 25 to 50% of persons with schizophrenia as falling in the variably defined "deficit range" for working memory (295–299).

Several lines of evidence suggest that the working memory deficits are, in part, heritable. Twin studies of unaffected and discordant (for schizophrenia) MZ and DZ twin pairs indicate that genetic influences in the schizophrenia-related working memory deficits are prominent (300–302). 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 (298, 303, 304), although this finding is not observed consistently (305, 306).

Working memory deficits are more common among the unaffected relatives (compared with control subjects) of schizophrenic individuals who have deficits themselves (307). The effect size for this observation is relatively small, such that substantial sample numbers are required to have adequate power. If only those studies that examined, at minimum, approximately 50 relatives of approximately 50 control subjects are considered (307–311), then there is a preponderance of data suggesting that unaffected relatives (of schizophrenic individuals) have some of the neuropsychological deficits seen in the 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, trail-making, 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 control subjects (312, 313).

The preponderance of data suggests that neuropsychological/cognitive deficits in schizophrenia are present more often among affected persons, compared with control subjects. There are data to indicate that the measures are heritable. Finally, most larger studies find that nonpsychotic relatives of schizophrenic individuals score more poorly on various neuropsychological tests compared with control subjects. 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 (314). The P50 wave is a positive deflection (recorded by scalp electrodes) occurring 50 ms after an auditory stimulus, typically a single click. When two such clicks are presented, the second occurring approximately 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. 29.2 and Color Plate 8, following p. 650). 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, i.e., there is no amplitude reduction, as shown below (Fig. 29.2). This is interpreted as a failure of sensory gating.

The P50 abnormality is found more often among individuals with schizophrenia, compared with control subjects (315, 316), although this is not universally confirmed (317, 318). The P50 abnormality is found more frequently among the relatives of persons with schizophrenia, compared with control subjects (319, 320). It is a partially heritable characteristic, based on twin studies (321, 322). 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 (323–325). The chromosome 15 location is a confirmed linkage region for schizophrenia (323, 326, 327), thereby lending added confidence to this line of investigation.

Although there is ample evidence that the P50 is partially under genetic control (321, 322), there is also substantial evidence that P50 parameters are influenced by environ-

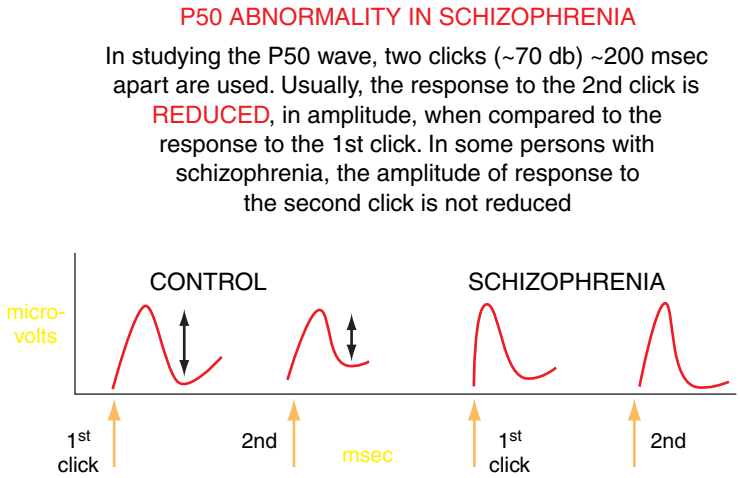

FIGURE 29.2. P50 abnormality in schizophrenia. In studying the P50 wave, two clicks (~70 db) approximately 200 msec apart are used. Usually, the response to the second click is reduced in amplitude when compared with the response to the first click. In some people with schizophrenia, the amplitude of response to the second click is not reduced (*see* Color Plate 8, following p. 650).

mental forces. For example, smoking or administration of nicotine may "normalize" an abnormal P50 test (328, 329). The finding becomes more intriguing when it is recalled that as many as 80% of individuals with schizophrenia are daily smokers (330). Additionally, there is evidence that atypical antipsychotic medications can "normalize" abnormal P50 testing (331–334). 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 that may provide pathways from gene variants to endophenotypes, or from endophenotypes to key symptom clusters or subtypes of disorders.

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.

15. Somatization Disorder

In a family history study, Coryell (335) 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 of 212 relatives) in the first-degree relatives of the Briquet's syndrome probands compared with control values of 2.3% (5 of 214 relatives) and 2.5% (7 of 283 relatives) ($P < 0.01$).

In a family study of Briquet's syndrome, Guze et al. (336) reported a significantly increased risk for Briquet's syndrome among the first-degree female relatives of Briquet's syndrome probands (7 of 105 relatives), compared with female relatives of control probands (13 of 532 relatives). Additionally, they reported an increased risk for antisocial personality among the male (18 of 96 relatives) and female (9 of 105 relatives) relatives of the Briquet's syndrome probands, compared with the risk for male (44 of 420 relatives) and female (14 of 532 relatives) relatives of control subjects.

Torgersen (337) studied 14 MZ twin pairs and 21 DZ twin pairs in which one member had a somatoform disorder (including somatization disorder, conversion disorder, psychogenic pain disorder, and hypochondriasis). Of MZ twin pairs, 29% were concordant for some type of somatoform disorder, compared with 10% of DZ twin pairs (not a significant difference in this small sample).

15.1. Adoption Studies

In an analysis of a large Swedish adoption cohort, Sigvardsson et al. (338) 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. (68) 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 on 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 (339) and by Torgersen in (340). 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.

16. Tourette's Syndrome

16.1. Twin Studies

Price et al. (341) studied 43 pairs of same-sex twins, 30 MZ and 13 DZ pairs. MZ twin concordance was 77% for any tics, compared with 23% for DZ twins. For Tourette's syndrome per se, the MZ concordance rate was 53%, compared with the DZ rate of 8%. These are all significant differences.

Pauls et al. (342) studied 338 biological relatives of 38 Tourette's probands, 21 adoptive relatives, and 22 relatives of healthy control subjects. Among the biological relatives, 28 (8.3%) of 338 had Tourette's syndrome, whereas 55 (16.3%) of 338 had chronic tics and 32 (9.5%) of 338 had OCD. These risks are all significantly greater than the risks for the 43 relatives of control subjects.

Baron et al. (343) reported that the transmission of Tourette's syndrome and chronic tics was consistent with a single locus model. Kidd and Pauls (344) were unable to differentiate between a single locus model and polygenic models.

16.2. Molecular Studies

A collaborative effort to use systematic genomic screening to find genes causing Tourette's syndrome has been underway for several years. Recent results implicate chromosome 2p (345). Rare mutations in the dendritic growth protein, SLITRK1 (chromosome 13q), have been associated with this condition (346).

17. Genetic Counseling

Empirical data for genetic counseling is summarized in Table 29.7. These data assume that the other parent is unaffected. The percentages in parentheses after the family history provide the unselected general population risk. For example, the general population lifetime risk for unipolar illness (when defined to include incapacitation or severe impairment) is 8%. If an individual has a unipolar parent, their lifetime risk is double the general population risk, or 16%. Such individuals are also at fourfold 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 years. Fully 50% of bipolar individuals develop an initial episode (either depressive or manic) before age 20 years. 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, their risk is substantially less than 9% to develop bipolar disease. An estimate of approximately 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 references (230) and (111). 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 usefulness within the next decade.

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Novel Mechanisms of Drug Treatment in Psychiatry

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Abstract In this chapter, we review potential novel mechanisms of drug treatment in psychiatry. We emphasize novel molecular targets and potential indications for a number of psychiatric diseases, including depression, anxiety, and schizophrenia. In many cases, novel mechanisms have only been validated in preclinical model systems, and we suggest increasing efforts for providing early stage clinical trials of medications for drugs with novel mechanisms of action.

Keywords Anxiety · Bipolar disorder · Depression · Novel drug target · Obsessive–compulsive disorder · Schizophrenia

1. Introduction

The increasing awareness that neuropsychiatric disorders as a category exact a high economic burden on the healthcare system worldwide has been fueling the continued demand for novel and effective therapeutic treatments for these disorders. The challenges facing the development of neuropsychiatric drugs are manifold, but perhaps the most salient one remains the dearth of preclinical models that accurately reflect their human equivalents. Given the costly nature of drug development in general, it is not surprising that the pharmaceutical industry has resorted to a commercially viable strategy of pursuing novel indications for already approved drugs, a tactic known as repurposing (1, 2). Nevertheless, the pace of central nervous system (CNS) drug discovery will accelerate because of concomitant progresses made in neuroscience and genomics. Advances in neuroscience in the past several decades have tremendously expanded our knowledge of the psychopathophysiology and, in the process, engendered a plethora of potential drug targets, some of which have gone on to prove remarkably successful in the pharmaceutical market. With the completion of the human genome-sequencing project, a growing bioinformatics capability to mine complex genomic database with partial deduction of gene function provides the promise to further expand the availability of novel classes of CNS drugs. The efficient application of high-throughput screening of chemical libraries greatly expedites the identification of small molecules interacting with these potential targets. Here, we summarize the mechanism of action of novel approved drugs as well as potential drugs in the treatment of schizophrenia and mood disorders, including unipolar depression, bipolar disorder, anxiety, and obsessive–compulsive disorders.

2. Depression

2.1. The Monoamine Approach

The working model of depression in the last half of century operates under the hypothesis that depression results from central disturbance in the monoamine system, including serotonin (5-HT), norepinephrine (NE), and/or dopamine (DA) transmission (3, 4). The antidepressant efficacies of medications that modulate monoaminergic neurotransmission are well established:

1. Tricyclic antidepressants (TCAs) inhibit presynaptic reuptake of norepinephrine and serotonin. TCAs also block various muscarinic cholinergic receptors and histamine receptors, causing anticholinergic side effects (e.g., mild cognitive disturbance, blurred vision, dry eyes, dry mouth, tachycardia, constipation, and urinary hesitancy) as well as antihistamine side effects (e.g., sedation and weight gain), respectively (5).
2. Monoamine oxidase (MAO) inhibitors increase CNS levels of serotonin, norepinephrine, and dopamine (6). Irreversible and nonselective MAO inhibitors are particularly effective in the treatment of depression in the elderly, comorbid with phobic anxiety, and atypical depression (15–20% of major depression that is characterized by

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hysterical traits, hypersomnia, eating disorder, fatigue, and sense of rejection). The main limiting factors of MAO inhibitors include a tyramine-free diet and potentially dangerous drug–drug interactions. Given that inhibition of mucosal MAO isozymes likely contribute to the dietary restrictions, a transdermal delivery system for the MAO inhibitor, selegiline, was developed and demonstrates antidepressant efficacy in three of five placebo-controlled trials (7).

3. Selective serotonin reuptake inhibitors (SSRIs), such as fluoxetine (Prozac), paroxetine (Paxil), and sertraline (Zoloft), preferentially increase serotonin levels in the CNS, and have relatively benign side effect profile when compared with TCAs and MAO inhibitors because of minimal effects on the cholinergic and histaminergic systems. The shortcomings of SSRIs include other side effects (e.g., gastrointestinal distress, insomnia, nervousness, agitation, and sexual dysfunction) that lead to discontinuation in a substantial minority of patients, failure of therapeutic response in approximately one third of the patient population, and inability to reduce suicide rates (8).
4. A more recent class of dual-acting serotonin/norepinephrine reuptake inhibitors (SNRIs), including venlafaxine (Effexor) and duloxetine (Cymbalta), seem to have better tolerability than TCAs with a faster clinical onset of actions than SSRIs, and are reportedly more effective in managing depressed patients who have failed treatment with other classes of antidepressants (9, 10).

2.1.1. Subtype-Selective Serotonin Approaches

Because there are at least 14 different serotonin receptors, the mood-modulating effects of SSRIs are likely mediated by a subset of these receptors. On the other hand, serotonin receptors that may be distinct from those that mediate antidepressant or anxiolytic activities are likely responsible for the undesired side effects of SSRIs.

Nefazodone is a weak inhibitor of serotonin and norepinephrine reuptake, but a potent blocker of the 5-HT_2 family of serotonin receptors. The effectiveness of nefazodone in the treatment of chronic depression is offset by its rare association with lethal hepatitis. Trazodone, which is structurally similar to nefazodone, does not cause hepatic toxicity, but is limited by its major side effect of sedation (9). Some SSRIs are weak 5-HT_{2C} receptor antagonists, and chronic SSRI treatment is known to cause the desensitization of 5-HT_{2C} receptors (11). Although there are preclinical data supporting the idea that 5-HT_{2C} antagonism augments the neurochemical and behavioral effects of SSRIs, 5-HT_{2C} receptor antagonism alone, interestingly, has no significant effect on synaptic levels of serotonin. That 5-HT_{2C} receptor-null mutant mice exhibit enhanced neurochemical and behavioral response to fluoxetine when compared with their wild-type litter mates argues for a strategy combining SSRIs and 5-HT_{2C} antagonists (12).

The 3 to 5 weeks of lag time between the initiation of antidepressant treatment and the onset of full clinical efficacy reflects the time required for desensitization of the receptors regulating monoamine release. In the case of SSRIs, the elevation in synaptic serotonin after acute treatment activates postsynaptic 5-HT_{1A} autoreceptors in the somata and dendrites within serotonergic neurons from the dorsal raphé nuclei, inhibiting the firing of serotonergic neurons and dampening subsequent 5-HT release. Continued exposure to SSRIs desensitizes the 5-HT_{1A} autoreceptors, producing more pronounced elevations in serotonin levels when compared with acute treatment (13). Thus, a strategy combining SSRIs with 5-HT_{1A} receptor antagonists is predicted to expedite the rise in central serotonin levels and should, theoretically, accelerate the onset of antidepressant efficacy. In microdialysis studies, coadministration with presumably selective 5-HT_{1A} antagonists (e.g., WAY-100635) augments SSRI- and SNRI-induced changes in cortical serotonin levels (14). 5-HT_{1A} antagonism potentiates the antidepressant-like behavioral effects of SSRIs in preclinical models, and 5-HT_{1A}-deficient mice exhibit antidepressant-like responses (15, 16), but there has been no definitive demonstration of the clinical benefit of combining SSRIs with 5-HT_{1A} antagonists (12). Recent evidence indicates that WAY-100635 and its major metabolite WAY-1000634 are potent D_4 partial agonists (17), suggesting that we may have to reexamine previous studies that attribute the actions of WAY-100635 solely to 5-HT_{1A} antagonism.

2.1.2. Triple Monoamine Uptake Blockers

Dopamine plays a role in motivation and responsiveness to salient stimuli (18). Decreased motivation and loss of responsiveness are observed in depressed humans. Anhedonia, a core symptom of depression, likely results from deficits in dopaminergic transmission, and there is limited evidence that dopamine agonists improve depressive symptoms in patients refractory to conventional antidepressants (12). In the Parkinson patient population, in whom there is a high comorbidity with depression, the cortical level of dopamine in addition to norepinephrine and serotonin is reduced (19). Selective dopamine reuptake inhibitors (e.g., GBR12909) have demonstrated antidepressant efficacy in animal models of depression such as the forced swim test (18). Coadministration of a dopamine (D_1R, D_2R, or D_3R) agonist with SSRIs significantly improves the rodent's performance on the forced swim test when compared with SSRI alone. Inhibitors that selectively block norepinephrine, 5-HT, and dopamine transmission (e.g., DOV 21947 and DOV 216303) have demonstrated antidepressant properties in preclinical animal models (9). Thus, a strategy that increases dopamine neurotransmission will likely augment traditional monoamine antidepressants, especially when anhedonia and apathy are the primary symptoms (18).

2.1.3. Atypical Antidepressants

Atypical antidepressants seem to modulate the monoamine system of neurotransmission despite their poorly understood mechanisms of action. Activation of presynaptic α_2-adrenergic autoreceptors located on both norepinephrine and dopamine neurons as well as local α_2-adrenergic receptors in the dorsal raphé nuclei, blunts noradrenergic, dopaminergic, and serotonergic responses, respectively. Depending on the brain region, α_2-receptor antagonists that are administered via microdialysis augment the ability of other classes of antidepressants to increase extracellular levels of norepinephrine, dopamine, and serotonin (12). Mirtazapine (Remeron), a nonselective α_2-receptor antagonist that also acts on several presynaptic and postsynaptic serotonin receptors, possesses modest antidepressant activity and causes sedation and weight gain, likely via blockade of H_1 histamine receptor (5, 20). Bupropion (Wellbutrin) inhibits the reuptake of norepinephrine and dopamine, and is an effective antidepressant with a decreased incidence of side effects of sexual dysfunction and weight gain, but it slightly decreases the seizure threshold (12).

2.2. Strategies to Target Excitatory Amino Acids

Neuroimaging studies point to the involvement of two critical circuits in the mood disorders (21). The first is the limbic–thalamic–cortical (LTC) circuit, comprising the amygdala, the medial dorsal thalamus, and the orbital and medial prefrontal cortex, regions that are interconnected by excitatory glutamatergic projections. The second is the limbic–cortical–striatal–pallidal–thalamic (LCSPT) circuit, including the striatum and pallidum in addition to the components of the LTC. Interestingly, neurological conditions (e.g., Huntington's disease, Parkinson's disease, stroke, and brain tumor) that involve lesions in these two circuits are associated with a high incidence of mood disturbance (22). Pathological hyperactivity of the LTC and LCSPT circuits in mood disorders is likely associated with increased glutamatergic activity, which could result in cytotoxicity in these regions by activation of calcium-dependent enzymes and the generation of oxygen free radicals. The anatomically restrictive loss of neuropil in these areas further supports the involvement of glutamate toxicity in the affective circuitry (23, 24). Thus, the complexity of the glutamate signaling system provides great potential for novel therapeutic strategies in mood and other CNS disorders (21).

2.2.1. NMDA Receptor

The *N*-methyl-D-aspartate (NMDA) receptor is an ionotropic glutamate receptor with the greatest distribution in the cortico–limbic regions of the brain. The NMDA receptor is an oligomer comprising the NR1 subunit essential for channel function and several other subunits such as NR2A–NR2D that associate to form the channel. Modulatory sites on the NMDA receptor include a glycine-sensitive binding site (stimulatory), two voltage-sensitive magnesium and zinc sites (involved in blocking NMDA responses), and two polyamine sites (either stimulatory or inhibitory) (25).

Chronic antidepressant treatment downregulates NMDA receptors and reduces glutamate release through presynaptic mechanisms. Excessive glutamate transmission, which could be precipitated by stress, likely plays a central role in the atrophy of hippocampal CA3 pyramidal neurons, whereas reduced NMDA glutamate receptor activity prevents stress-induced hippocampal atrophy (21). In animal models, NMDA antagonists (e.g., MK-801, memantine, ketamine) that reduce glutamatergic transmission have demonstrated antidepressant-like effects comparable to TCAs (9, 21). The main limitations to the therapeutic usefulness of competitive and uncompetitive NMDA receptor antagonists are the side effects of psychosis and memory loss. Clinical trials are now under way assessing the antidepressant potential of the weak NMDA receptor antagonist, memantine, and the glutamate release inhibitor, riluzole, two US Food and Drug Administration (FDA)-approved compounds that were initially developed for cognitive enhancement and neuroprotection, respectively (26).

2.2.2. AMPA and Kainate Receptors

AMPA and kainate receptors with a distribution similar to NMDA receptors mediate the majority of fast excitatory glutamatergic transmission and modulate synaptic strength (27). The AMPA receptor comprises the GluR1–4 subunits with allosteric modulatory sites that represent potential drug targets for fine-tuning glutamatergic activity (28).

AMPA receptor-positive modulators, or AMPAkines, allosterically augment AMPA receptor activity in the presence of agonist (e.g., glutamate, AMPA) and reduce the rate of agonist-mediated receptor desensitization (29). In animal models such as the forced swim and tail suspension tests, AMPAkines (e.g., LY392098 and LY451646) display dose-dependent antidepressant-like effects comparable to TCAs and SSRIs (21, 26). AMPAkines upregulate the expression of brain-derived neurotrophic factor (BDNF) in vivo, and rapidly promote neurogenesis and neuronal sprouting in the hippocampus (30). In contrast, monoamine-based antidepressants increase BDNF expression only after chronic treatment (21). Because BDNF plays a central role in antidepressant actions (see section 2.5.1.), AMPAkines with potentially faster onset of clinical efficacy could represent a bridge therapy to monoamine-based antidepressant therapy.

2.2.3. Metabotropic Glutamate Receptors

The metabotropic glutamate receptors (mGluRs) are G protein-coupled receptors that exert long lasting modulatory effects on glutamatergic neurotransmission. Based on effector coupling and molecular homologies, they are divided into three groups: Group I (mGluR1 and mGluR5), Group II

(mGluR2 and mGluR3), and Group III (mGluR4, mGluR6–mGluR8) (1, 12).

The predominantly postsynaptic Group I metabotropic receptor subtypes are coupled to the G_q protein and phospholipase C (1). Negative allosteric modulators that antagonize the generally excitatory Group I receptors have demonstrated therapeutic potentials in animal models of depression and anxiety disorders. Knockout studies also predict that antagonists of the mGluR5 receptor will possess anxiolytic properties (21). Group II receptor subtypes, which are found on presynaptic and postsynaptic sites in the forebrain and limbic regions, inhibit adenylyl cyclase and reduce endogenous glutamate release under conditions of glutamate excess (1). Activation of presynaptic Group II receptors serves to decrease glutamate release via negative feedback, whereas activation of postsynaptic receptors reduces neuronal excitability. In preclinical studies, mGlu2/3 agonists have anxiolytic, antipsychotic, and neuroprotective properties, whereas mGluR2/3 antagonists produce antidepressant-like effects in part by facilitating serotonergic neurotransmission and stimulation of postsynaptic AMPA receptors (1, 12). The predominantly presynaptic Group III receptors are negatively coupled to adenylyl cyclase, and decrease glutamate signaling within the hippocampus and hypothalamus (21). Whereas mGluR7-deficient mice display antidepressant-like and anxiolytic-like behaviors, mGluR8-deficient mice demonstrate anxiety-like behavior (31, 32). Few compounds selectively target Group III receptors (33).

2.3. Gamma-Aminobutyric Acid

Gamma-aminobutyric acid (GABA) is the primary inhibitory neurotransmitter in the CNS. Regulation of GABA neurotransmission involves a complex interplay involving the biosynthetic enzyme (glutamic acid decarboxylase [GAD]), the catabolic enzyme (GABA transaminase), and the GABA transporters. The effects of GABA are mediated by the ionotropic $GABA_A$ receptors, which cause rapid membrane depolarization, and the metabotropic $GABA_B$ receptors, which cause hyperpolarization of postsynaptic neurons and inhibition of neurotransmitter release from presynaptic nerve terminals (34, 35).

Enhanced $GABA_A$ receptor activity plays a central role in the antidepressant-like effects that are mediated by neuroactive steroids (e.g., allopregnanolone) (36). On the other hand, evidence that selective $GABA_B$ antagonists (e.g., CGP36742, CGP56433) exert antidepressant-like effects in preclinical models, and that $GABA_{B1}$-knockout mice display an antidepressant-like phenotype support the potential of $GABA_B$ receptor antagonism as a novel antidepressant therapy (12).

2.4. Strategies to Target Central Peptides

2.4.1. Substance P

Abundantly expressed in the CNS, Substance P belongs to the tachykinin family of neuropeptides, whose members also include neurokinin A and neurokinin B (37). Substance P binds to several neurokinin receptor subtypes, including NK1, NK2, NK3, NKA, and NKB. In addition to its function of pain modulation in the spinal cord, Substance P regulates an array of stress-related behaviors. Furthermore, cerebral spinal fluid (CSF) levels of Substance P are elevated in depressed patients, and clinical response to antidepressants are associated with decreased CSF levels of Substance P (38).

Several lines of evidence support the antidepressant potential of a strategy of NK1 antagonism. First, Substance P inhibits monoamine neurotransmission primarily through NK1, a G_q protein-coupled receptor. NK1-selective antagonists have demonstrated antidepressant properties in a number of animal models, and, curiously, have a delayed onset of action similar to that of monoamine-based antidepressants (38, 39). NK1-deficient mice exhibit anxiolytic and antidepressant-like behavioral phenotypes (40). Second, Substance P elicits a behavioral and physiological stress response that could be attenuated by NK1 antagonists, which enhance firing rates of dopaminergic, noradrenergic, and serotonergic neurons (41). Finally, genetic or pharmacological blockade of NK1 induces hippocampal neurogenesis, which is postulated to prevent depression (26). Even as it came as a major disappointment that the NK1 antagonist Aprepitant failed to demonstrate clinical efficacy in at least five large-scale phase III trials, other NK1-selective antagonists (e.g., L-759274 and CP-122721) have shown clinical evidence of antidepressant efficacy as well as a benign side effect profile (9, 38).

2.4.2. Melanin-Concentrating Hormone

Melanin-concentrating hormone (MCH) is a 19-amino acid cyclic neuropeptide secreted from nuclei in the lateral hypothalamus. MCH, with its broad projections in the CNS, modulates mood, arousal, feeding, energy homeostasis, sensorimotor integration, and autonomic control. Interestingly, MCH increases the activity of hypothalamic–pituitary–adrenal (HPA) axis (42, 43).

MCH mediates its biological activities primarily through two receptors, of which, the G_i protein-coupled MCH_1R, with the highest concentration in the nucleus accumbens, is better characterized (44). Local administration of MCH into the nucleus accumbens or overexpression of MCH produces depression-like behaviors in animal models. Conversely, MCH1-R antagonists, when administered systemically or directly into the nucleus accumbens, display antidepressant-like properties in the forced swim test (45), a phenotype that is also observed in MCH-deficient mice. Thus, MCH antagonists likely exert their antidepressant effects by disrupting

MCH receptor signaling in the nucleus accumbens. Incidentally, MCH_1R antagonists are also anti-obesity agents that could be particularly beneficial in the subset of depressed patients who are overweight (46).

2.4.3. Arginine Vasopressin

Arginine vasopressin (AVP), a cyclic nonapeptide that is synthesized in the paraventricular and supraoptic hypothalamic nuclei, mediates a variety of peripheral and central functions. When released into the peripheral circulation, AVP regulates vasoconstriction, glycogen metabolism, and fluid homeostasis. The central vasopressin system plays a role in mood, memory, sleep, pain sensitivity, social behaviors, biological rhythm, thermoregulation, and autonomic function. Several lines of evidence support the involvement of AVP in mood disorders: 1) stress stimulates the release of AVP, which may contribute to abnormalities in the HPA axis; 2) hyperactivity in the central vasopressin system has been reported in clinical depression; and 3) SSRI treatment has been reported to normalize vasopressin levels (26, 47).

AVP mediates its effects through a group of phylogenetically related G protein-coupled receptors, of which the V1b (also known as V3) receptor is a potential drug target in mood disorder. V1b receptors modulate the function of corticotrophs in the anterior pituitary, regulating the stress response of the HPA axis (12). Although V1b-deficient mice surprisingly display normal stress responses, selective blockade of V1b receptor (e.g., SSR 149415) in animal models demonstrates antidepressant-like properties, and attenuates stress-induced endocrine, neurochemical, and autonomic changes (26).

2.4.4. Corticotropin-Releasing Factor

Corticotropin-releasing factor (CRF) is a 41-amino acid peptide that integrates the endocrine, autonomic, immune, and behavioral responses to stress. Hypothalamic neurons in the paraventricular nucleus release CRF into the hypothalamo–hypophysial portal system, where it stimulates the anterior pituitary to release the adrenocorticotropin hormone (ACTH), which, in turn, stimulates the secretion of glucocorticoid hormone from the adrenal cortex to the systemic circulation. The HPA axis is essential to an individual's capacity to cope with stress. CRF projections are also found in extrahypothalamic sites, including limbic regions of the affective circuits (e.g., amygdala, bed nucleus of the stria terminalis) involved in behavioral responses to stress, and brain stem nuclei (e.g., locus coeruleus, nucleus of solitary tract) involved in controlling autonomic response to stress.

Neuronal degeneration in the affective circuitry may provide the physical link between stress and depression (48). In animal models, steroid injection and exposure to acute and chronic stress seem to disrupt dendritic morphology and synaptic connectivity in the prefrontal cortex, amygdala, and hippocampus, as evidenced by dendritic shortening and spine loss, changes that can be prevented by antidepressant treatment (49, 50). Imaging studies suggest that hippocampal atrophy is associated with repeated depressive episodes and stress (51, 52). One theory of depression postulates that it arises from dysfunctional synaptic plasticity in response to stress. Reduction in BDNF expression and cellular volume in the hippocampus has been found in posttraumatic stress disorder as well as subtypes of depression in which there is HPA axis hyperactivity, and adrenalectomy prevents stress-induced neuronal atrophy (26, 53). The working hypothesis is that stress reduces cellular resilience (or the property of being able to return to original form), rendering certain neurons more vulnerable to insults such as ischemia, hypoglycemia, and excitatory amino acid toxicity (21,54). In the hippocampal dentate gyrus, stress likely not only promotes cell death but also inhibits the birth of new granule cell neurons.

CRF likely plays a central role in precipitating depression in susceptible individuals under psychological and physiological stress. Depression is associated with findings of hyperactivity in the HPA axis, specifically, elevated levels of CRF in CSF, increased CRF messenger RNA (mRNA) expression and increased numbers of CRF neurons in the paraventricular nucleus of the hypothalamus, and overall increased CRF activity (12). Many of these changes could be reversed by successful antidepressant treatment with TCAs and SSRIs (55). Overexpression of CRF in transgenic mice or direct administration of CRF into the CNS produced a depression-like phenotype (26).

CRF mediates its wide range of effects through CRF1 and CRF2, both of which are G_s protein-coupled receptors. CRF1 is the receptor subtype expressed predominantly on the corticotrophs of the anterior pituitary, and, thus, mediates ACTH release, the key function of CRF in the HPA axis (56). In preclinical models, CRF1 antagonists block the behavioral and endocrine responses to stress and display antidepressant-like properties. CRF1 receptors are also expressed throughout the limbic regions, where selective blockade attenuates behavioral responses to stress (26). The only CRF1 antagonist (e.g., R121919) that entered clinical trials to date was discontinued because of hepatotoxicity (12). CRF2 has a more restricted expression in the CNS and a lower affinity for CRF than CRF1, and CRF2 antagonists are predicted to cause fewer side effects via the HPA axis. Interestingly, although CRF2-deficient mice display anxiety-like phenotype, CRF2 antagonists have anxiolytic and some antidepressive properties in animal models (26). Taken together, an antidepressant strategy of reducing CRF activity in depressed patients will likely prove promising, but it is not at all clear, based on existing evidence, that CRF antagonists would be any more effective than currently available treatments (10).

Another antidepressant strategy targeting the HPA axis involves inhibition of the glucocorticoid receptor, which might be effective in treating depression with psychotic features. Selective overexpression of glucocorticoid receptors in the forebrain produces depression-like and anxiety-like

phenotypes when transgenic mice are placed under stress (57). Mifepristone, which inhibits the glucocorticoid receptor as well as the progesterone receptor, is currently in Phase II clinical trials for psychotic major depression. Metyrapone, an inhibitor of glucocorticoid synthesis, has also shown promise as an adjunct to standard antidepressant (12).

2.5. Neurotrophin

Neurotrophins comprise a family of proteins including nerve growth factor (NGF), BDNF, and neurotrophins (NT)-3, -4/5, and -6. Proneurotrophins are enzymatically processed to create mature neurotrophins that bind to Trk receptor tyrosine kinases (58). Although the low-affinity p75 receptor is common to all neurotrophins, the high-affinity Trk receptors are associated with specific neurotrophins: 1) TrkA binds preferentially to NGF; 2) TrkB binds to BDNF and NT-4/5; 3) TrkC binds to NT-3. These associations are likely oversimplified because NT-3 also binds to TrkA and TrkB with low affinity (58).

Interaction of mature neurotrophins with Trk receptors promotes neuronal growth, differentiation, and survival, and modulates synaptic plasticity (58). The prosurvival effects of neurotrophins result, in large part, from activation of the mitogen-activated protein kinase (MAPK) signaling pathway and the phosphatidylinositol-3 kinase (PI3K)–Akt pathway, and from inhibition of cell death cascades. Reduced expression of neurotrophins (e.g., BDNF) and hippocampal neurogenesis are found in animal models of depression such as the learned helplessness and restraint stress models. Conversely, chronic antidepressant treatments upregulate neurotrophin expression and signaling. Blockade of hippocampal cell proliferation with irradiation prevents antidepressant-mediated effects. Thus, neurotrophin-mediated proliferation of hippocampal progenitor cells is thought to be one of the final common mechanisms of antidepressant effects (26, 59). Interestingly, SSRIs amplify the number of neural progenitors, specifically, cells generated in the second stage of neurogenesis (60). Taken together, augmenting neurotrophin activity is a potentially novel antidepressant strategy.

2.5.1. Brain-Derived Neurotrophic Factor

Neurotrophin-based antidepressant research has focused on BDNF, which, in addition to its effect on neuronal viability, mediates complex physiological actions that include facilitation of presynaptic release of acetylcholine, glutamate, and GABA; strengthening of excitatory neurotransmission by enhancing phosphorylation of NMDA receptors and augmenting the amplitude of AMPA receptor-mediated miniature excitatory postsynaptic current; and strengthening of inhibitory neurotransmission by increasing the frequency of inhibitory postsynaptic currents and increasing the size of GABAergic synaptic terminals (21, 61). Several lines of evidence support a novel antidepressant strategy of promoting BDNF-mediated signaling (62). First, local injection of BDNF into the rodent hippocampus produces antidepressant-like effects in the forced swim and learned helplessness tests (63). Second, BDNF and TrkB heterozygous knockout mice that displayed no abnormal behavior at baseline were resistant to the effects of antidepressants (26). Similarly, conditional deletion of forebrain BDNF did not produce a baseline depressive phenotype, but the mice had an attenuated response to SSRI antidepressant administration in the forced swim test (64). Finally, depressed patients without treatment have low serum BDNF levels, which are restored by antidepressant treatment. In postmortem studies, suicide victims have reduced TrkB and BDNF mRNA expression in the hippocampus when compared with control subjects (12).

Currently, no antidepressant therapy directly targets neurotrophins. Several phase III clinical trials using subcutaneous injection of BDNF, insulin-like growth factor (IGF)-I, or ciliary neurotrophic factor (CNTF) to treat symptoms of amyotrophic lateral sclerosis did not demonstrate clinical efficacy, likely because of the failure of these neurotrophic factors to crossing the blood–brain barrier. Furthermore, BDNF-mediated antidepressant-like effects seem to be anatomically restricted to the hippocampus, raising caution that BDNF-based antidepressants might produce competing effects in different brain regions. Infusion of BDNF into the ventral tegmental area–nucleus accumbens (VTA-NA), the dopamine reward circuit, produces a depression-like phenotype in animal models. Viral-mediated local deletion of BDNF from the ventral tegmental area demonstrated antidepressant-like effect in a social defeat model (65). Although efforts are underway exploring alternative drug delivery systems to the brain, such as the use of small molecule peptides that would bind to specific neurotrophin domains, there are also interests in targeting the multiple components in the neurotrophin signaling cascades that show more restricted patterns of expression (12, 26).

2.5.2. cAMP Response Element-Binding Protein

The BDNF gene has at least four promoters, and the transcription factor cAMP response element-binding protein (CREB) plays a major role in regulating the gene expression of BDNF (66). In both animal and postmortem human studies, chronic antidepressant treatments seem to not only upregulate BDNF expression but also increase CREB levels and CREB phosphorylation in the hippocampus and cortex (21, 67). Local induction of CREB in the hippocampus produces an antidepressant-like effect in the forced swim test (26). As in the case with BDNF, selective induction of CREB expression in the nucleus accumbens produces the opposite effect. Interestingly, stress promotes CREB-mediated induction of dynorphin, a kappa opioid peptide, in the nucleus accumbens, and produces depression-like behaviors similar to anhedonia. Administration of kappa receptor antagonists that block dynorphin action, either systemically or directly into the nucleus accumbens, exert antidepressant effects (68, 69).

2.5.3. Phosphodiesterases

Phosphodiesterases (PDEs) catalyze the degradation of cAMP. By preventing the breakdown of this second messenger, inhibition of PDE enhances the activity of CREB and likely neurotrophin signaling. Specifically, PDE4, with four subtypes, each of which is encoded by a different gene with multiple splice variants of each subtype, offers potential targets for novel antidepressant development. Rolipram, a nonselective PDE4 inhibitor, elevates BDNF levels in the hippocampus and exerts antidepressant-like effects in animal models. However, the initial limiting factor of Rolipram and its related PE4 inhibitors is the severe adverse effect of nausea and vomiting, which is secondary to inhibition of PDE4 in the brainstem. Furthermore, stimulation of the cAMP signaling and CREB activity in the VTA-NA has the undesired effect of promoting a depression-like phenotype, and its stimulation in the frontal cortical regions impairs cognitive function in aged animals. Given the potential complications of inhibiting PDE isoforms that are widely expressed in the brain, a successful PDE-based antidepressant strategy would selectively target PDE in the hippocampus (26).

2.5.4. Regulators of Apoptosis

The MAPK signaling cascade is activated by mood stabilizers and antidepressants, as well as by neurotrophins. MAPK activation promotes cell survival by increasing the expression of the anti-apoptotic protein, B cell lymphoma-2 (Bcl-2) and by decreasing the expression of the pro-apoptotic factor, Bcl-xL (12). In animal models, Bcl-2 promotes neurite sprouting, neurite outgrowth, and axonal regeneration, and seems to reverse stress-induced neuronal changes (62). Thus, drugs that target components of the apoptotic pathway in a brain region-selective manner might provide novel antidepressant approaches (70).

2.6. Other Novel Antidepressant Strategies

Here, we summarize a few more innovative approaches to antidepressant development that are perhaps less expected. Agomelatine, a mixed melatonin agonist and 5-HT_{2C} antagonist that resynchronizes biological rhythms, has proven to be a potent antidepressant with a low side-effect profile (71). Leptin, a weight-regulating hormone secreted by the adipose tissue, has receptors in the limbic region and can attenuate depression-like behavior in chronically stressed rats (72). Given that proinflammatory cytokines (e.g., interleukin-1β and 6, tumor necrosis factor-α, and interferon-γ) produces depression-like symptoms (e.g., anhedonia, reduced social interaction, and fatigue), a strategy promoting anti-inflammatory cytokines in the CNS may prove to be a novel antidepressant strategy (73).

3. Bipolar Disorder

3.1. Lithium and Anticonvulsants

Although lithium has been the traditional treatment of choice for stabilizing mood in bipolar disorders since the 1950s, it has a greater clinical efficacy than anticonvulsants such as carbamazepine (Tegretol) and divalproex (Depakote) (10, 74). There are some interesting reports that lithium and some of the anticonvulsants (e.g., divalproex) provide protective benefits in cortical neurons at least in part by 1) inducing BDNF expression and by activating BDNF/TrkB signaling, 2) by suppressing the activation of pro-apoptotic protein caspase-3, and 3) by inducing chaperone proteins (e.g., heat shock protein 70) and the anti-apoptotic protein Bcl-2 (75, 76). Lithium stimulates the proliferation of neuroblasts in vitro, and provides neurotrophic effects in human brain in vivo based on neuroimaging studies (21). As discussed in the case of unipolar depression, pharmacological strategies that enhance cellular resilience will likely provide long-term benefits in mood disorders.

3.1.1. Mitochondrial Dysfunction

Several lines of evidence suggest that mitochondrial dysfunction may contribute to the impaired cellular resilience in bipolar disorder. First, human imaging studies using magnetic resonance spectroscopy (MRS) reveals a metabolic shift from oxidative phosphorylation that is normally carried out in the mitochondria towards anaerobic glycolysis, as evident by the increased lactate, decreased *N*-acetyl-aspartate (NAA), and decreased intracellular pH (77). The implication of the reduced energy output is that neurons in bipolar patients are more predisposed to cellular injury. Second, mitochondria play a role in calcium homeostasis, and impaired calcium regulation is associated with bipolar disorder. Calcium excess could trigger the apoptotic cascade and promote neuronal death (21). Finally, microarray studies of postmortem brains demonstrate reduced expression of mitochondrial proteins in bipolar disorder, some of which regulate oxidative phosphorylation in the mitochondrial inner membrane or mediate ATP-dependent degradation of proteosome (78). There is currently no specific target in the mitochondrial system that has been directly linked to bipolar disorder. Interestingly, the neurotrophic protein, Bcl-2, which is upregulated by lithium, as discussed above, modulates mitochondrial function.

3.1.2. Circadian Gene Products

Abnormal circadian rhythms are thought to contribute to the pathogenesis of mood disorders, particularly, the rapidly cycling type of bipolar disorder. The master circadian generator in the brain likely resides in the suprachiasmatic nucleus (SCN) of the hypothalamus and matches the biological rhythm with the light and dark cycle (79). In the most simplistic model of generation of circadian rhythm at the

molecular level, the transcription factors Clk (clock) and Bmal (Brain and Muscle Arylhydrocarbon receptor nuclear translocator-like protein 1) dimerize and stimulate the expression of Per (Period) and Cry (Cryptochrome), both of which provide negative feedback to the activity of the Clk–Bmal dimer. Clk–Bmal, Per, and Cry further regulate the expression of other genes involved in the circadian rhythm. One of the molecular links between circadian rhythm and mood disorder is the Clock protein, which might play a role in the affective circuitry at the ventral tegmental area and nucleus accumbens (26, 80).

3.1.3. Glycogen Synthase Kinase-3

Glycogen synthase kinase (GSK)-3β has been found to regulate a variety of physiological activities, including apoptosis, glycogen synthesis, synaptic plasticity, and circadian rhythm. Its role in the circadian rhythm involves phosphorylation of circadian gene products (e.g., Period). Of the various current drugs that are known to modulate GSK-3 activity, the effectiveness of lithium and some anticonvulsants (e.g., valproate, lamotrigine) points to the potential of GSK-3 signaling cascade for novel drug targets for bipolar disorder (62). Transgenic mice overexpressing GSK-3β exhibit a mania-like phenotype (81). Pharmacologic and genetic manipulations of the GSK-3 signaling cascade have produced both antimanic and antidepressant effects (82). Furthermore, the role of GSK3 in apoptosis might also be relevant to bipolar disorder. Increased GSK-3 activity is pro-apoptotic, whereas inhibition of GSK-3 is anti-apoptotic. That lithium inhibits GSK-3 activity has led to the suggestion that this might be one of the mechanisms through which lithium exerts neuroprotective effects (21).

3.2. Histone Deacetylases

An important process of gene regulation involves the acetylation of histones, which decreases their affinity for DNA. A group of proteins known as histone deacetylases (HDACs) blocks the acetylation process and represses gene transcription. Several lines of evidence support the rather surprising notion that inhibition of HDAC might be a novel strategy for mood disorders (21). First, HDAC inhibitors have been found to have neuroprotective properties in vitro, and enhance memory in some neurological disorders such as Huntington's disease (83). Second, valproic acid, an anticonvulsant that is approved for mood stabilization in bipolar patients, has demonstrated, among its various actions, the ability to be a weak inhibitor of HDAC (84). Finally, antidepressant treatments might exert their effects in part by regulating histone acetylation in the brain. Imipramine, for example, reduces an HDAC isoform, HDAC5; whereas selective overexpression of HDAC5 in the hippocampus blocks the antidepressant-like effect of imipramine (85).

3.3. Protein Kinase C

The calcium and phospholipid-dependent protein kinase C (PKC) is involved in a number of intracellular signaling systems and plays a role in regulating gene expression. Increased PKC activity leads to impaired cognitive functions, whereas decreased PKC activity produces the opposite effect. Stress and psychostimulants that are capable of triggering manic episodes are known to enhance PKC activity. Conversely, mood stabilizers can reduce PKC activity (86). Thus, selective inhibitors of PKC are predicted to have mood-stabilizing properties (26).

3.4. Thyroid Hormone

Adjunctive thyroid hormone therapy has been used in refractory unipolar and bipolar disorders. Interestingly, bipolar patients with lower pretreatment thyroid levels are predicted to have a poor prognosis, even if the thyroid levels are within the normal limit, and mood fluctuation has been inversely linked to serum free thyroxine (T4) level (21). Triiodothyronine (T3) binds to nuclear thyroid hormone receptors, which have a high concentration in the limbic regions of the affective circuitry, including the amygdala and hippocampus (87). The T3-bound receptors are transcription factors that could induce the expression of neurotrophins and Trk proteins. Thyroid supplementation increases cAMP signaling and, thus, CREB activation. These are the two possible mechanisms whereby thyroid hormone exerts neurotrophic effects (88).

3.5. Glutamate-Based Strategies

Modulators of the glutamate neurotransmission present as novel targets for mood stabilization. The anticonvulsant lamotrigine (Lamictal), which is approved for the maintenance treatment of adults with bipolar disorder, inhibits excessive release of presynaptic glutamate. Riluzole (Rilutek), another inhibitor of glutamate release that has been approved for amyotrophic lateral sclerosis, also has antidepressant properties in both unipolar and bipolar disorders (89). The proposed mechanisms of riluzole include inhibition of sodium currents in axon terminals, activation of certain potassium channels, induction of BDNF expression, and facilitation of astrocytic uptake of glutamate.

4. Anxiety

The oldest anxiolytic drugs are sedative agents, such as barbiturates and benzodiazepines, which act on the GABA receptors and are severely limited by the adverse effects of sedation, dependence, ataxia, and memory impairments. Because anxiety is often comorbid with depression, antidepressants, particularly the SSRIs, have become the first choice for anxiety disorders (90).

4.1. Gamma-Aminobutyric Acid

Traditional anxiolytic agents such as benzodiazepines activate GABA receptor-mediated inhibitory neurotransmission. Various GABA receptor subtypes are widely present throughout the brain. The α_1 subunit of the $GABA_A$ receptor mediates the sedative effect but not the anxiolytic effect of benzodiazepine, whereas the α_2 and α_3 subunits of the $GABA_A$ receptor mediate the anxiolytic effect (91, 92). Thus, a novel strategy selectively targeting subtypes of the GABA receptor might produce the desired anxiolytic effect without the adverse effects of amnesia and sedation (8).

4.2. Glutamate-Based Strategies

Patients suffering from anxiety disorders misperceive benign stimuli as threatening. It is thought that a hyperactive amygdala with a weakened inhibition from the hippocampus and prefrontal cortex might contribute to these misperceptions (90). Functional neuroimaging studies have revealed an association between acute fear and amygdala activity in normal humans, but excessive amygdala activity is found in depression, panic disorder, social anxiety disorder, and posttraumatic stress disorder. Activation of the glutamatergic pathways that synapse on the lateral nucleus of the amygdala (LA) is essential for the acquisition, manifestation, and long-term memory storage of conditioned fear (93). NMDA receptor antagonists abolish the acquisition and extinction of conditioned fear when applied to the LA neurons in animal studies (94), and have demonstrated anxiolytic and antidepressant properties in limited clinical trials.

As discussed in section 2.4.4, stress induces dendritic atrophy and neuronal dysfunction in the prefrontal cortex, hippocampus, and amygdala, likely in a cortisol- and glutamate-dependent manner. During acute stress, internalization of glutamate receptors reduces the potential excitotoxic effects of excessive glutamate transmission. Reduction of dendritic length and spine number during chronic stress further reduces the total number of postsynaptic glutamate receptors that risk exposure to synaptic glutamate. Interestingly, fear learning functionally downregulates the NMDA receptors (95). Although dendritic remodeling is a long-term neuroprotective adaptation to stress, it diminishes synaptic connection and causes disconnection in neuronal circuitry. Disconnection of the amygdala from the tonic inhibition by the prefrontal cortex has been postulated as a contributing factor to anxiety (96). Long-term administration of different classes of antidepressants (e.g., TCAs, SSRIs, SNRIs, MAO inhibitors) decrease the glutamatergic neurotransmission without dendritic atrophy (90). A novel anxiolytic strategy is to minimize the cytotoxic effect of excessive glutamate neurotransmission and prevent stress-induced dendritic remodeling. Drugs that promote the internalization and reduce the cell surface expression of NMDA receptors may be potential anxiolytic agents (90).

The noncompetitive NMDA receptor antagonists have displayed anxiolytic efficacy in limited clinical studies, but are greatly limited by the significant adverse effects of psychosis and memory loss. The NMDA receptor has multiple allosteric regulatory sites. D-Cycloserine, a partial agonist at the glycine-sensitive site on the NMDA receptor, exerts anxiolytic-like effects in animal models and in a limited clinical study (97). Ifenprodil, a competitive antagonist at the stimulatory polyamine site, has anxiolytic properties and might provide distinct therapeutic advantages over the noncompetitive NMDA antagonists by avoiding loss of NMDA-dependent working memory (98).

4.3. Tissue Plasminogen Activator

In addition to its thrombolytic property, tissue plasminogen activator (tPA) mediates the effects of stress and CRF on the amygdala (99). Mice lacking tPA displayed reduced neuroendocrine responses to CRF and decreased anxiety-like behaviors. These actions are independent of plasminogen, suggesting that another substrate of tPA is the downstream target (100, 101). Interference with tPA or these other substrates might provide a novel anxiolytic or antidepressant approach (26).

4.4. Cannabinoid Receptor

Cannabinoid receptor (CB1), the predominant receptor for the endogenous cannabinoids in the brain, plays a role in regulating mood. CB1 antagonists may cause depression and anxiety as side effects (102), and drugs that promote the production of endogenous ligands for the receptor display anxiolytic and antidepressant properties in animal models (103, 104).

4.5. Neuropeptide Y

Neuropeptide Y (NPY) regulates feeding as well as response to stress. Several NPY receptors are broadly expressed in the forebrain. Manipulation of the NPY receptor might provide novel targets in the treatment of anxiety disorder and other mood disorders (105).

4.6. Serotonin Receptor

5-HT_{1A} receptors mediate adaptive responses to stress and may contribute to the cognitive disturbances found in stress-related disorders. 5-HT_{1A}-deficient mice display elevated anxiety, diminished exploratory activity, and less aggressive behavior than their wild-type litter mates (15, 16, 106). Chronic stress selectively downregulates the 5-HT_{1A} receptors in the hippocampus, and 5-HT_{1A}-deficient mice display impaired hippocampus-dependent learning and memory (107). Conditional expression of 5-HT_{1A} receptors in the hippocampus and cortex, but not in the raphé nuclei, rescues the behaviors of 5-HT_{1A} deficiency (108). 5-HT_{1A} partial

agonists (e.g., gepirone, buspirone) represent a class of non-addicting anxiolytic agents.

5-HT_{1B} receptors play a role in impulsivity, aggression, and addiction. 5-HT_{1B} receptor-deficient mice exhibit decreased anxiety-like behavior, reduced habituation (to stressful stimuli such as intruders), and more aggression than their wild-type litter mates (109). 5-HT_{1B} receptor-deficient mice develop a predilection for substances of abuse, such as ethanol and cocaine, and, even in the drug-naïve state, display behaviors resembling wild-type mice that have been chronically exposed to drugs of abuse (110, 111). Thus, 5-HT_{1B}-selective agonists are predicted to mitigate anxiety, aggression, and possibly compulsive behaviors associated with addiction.

5. Obsessive–Compulsive Disorder

5.1. Monoamine Strategies

Patients suffering from OCD encounter intrusive and irrational thoughts that they cannot dismiss, and engage in compulsive activities as maladaptive behaviors to relieve the associated anxieties (112). Because OCD is often comorbid with anxiety and depression, SSRI agents are generally considered the first-line treatment for OCD. However, higher doses of SSRIs and longer latency before the onset of clinical efficacy are often required in the treatment of OCD than in depression. Furthermore, a significant subset of OCD patients does not improve with the standard combination of SSRIs and cognitive behavioral therapy. Surprisingly, SNRIs, atypical monoamine-based antidepressants, and atypical antipsychotics have not demonstrated effectiveness in OCD (113).

5.2. Glutamate-Based Strategies

Given that obsessions are principally internal feelings and repetitive behaviors in animals are not always equivalent to compulsion secondary to obsession, OCD presents a particular challenge to interpretation in animal studies. Several lines of evidence suggest that abnormal glutamate neurotransmission may contribute to the pathogenesis of OCD (114). First, MRS studies have found dysregulation in glutamate transmission in the cortico–striato–thalamo–cortical (CSTC) circuits in OCD (115). The caveat is that the resolution of typical magnetic field strength is not high enough to differentiate glutamate from other small molecules or synaptic from extrasynaptic glutamate. Second, CSF glutamate levels are elevated in OCD patients (116). Third, the inhibitor of glutamate release, riluzole, has demonstrated limited clinical efficacy in OCD in addition to unipolar depression and bipolar disorder, neuropsychiatric disorders in which excessive glutamate activity plays a role (117). A double-blind, placebo-controlled trial of riluzole in OCD is in progress. Finally, glial cells release glutamate into the extrasynaptic space where it stimulates metabotropic glutamate receptors on glutamatergic axon terminals and reduces the synaptic release of glutamate. *N*-acetylcysteine (NAC), an antidote for acetaminophen toxicity, promotes the synaptic clearance of glutamate by glial cells, and has efficacy against OCD in limited trials (114,118).

6. Schizophrenia

Schizophrenia remains a debilitating disorder because antipsychotic drugs that became available in the last six decades have demonstrated only limited efficacy in alleviating symptoms of cognitive dysfunction (e.g., difficulty with abstraction, disorganized and tangential thinking), and the negative symptoms (e.g., blunted affect, anhedonia, apathy, alogia). The extent of cognitive dysfunction strongly predicts the functional outcome for schizophrenic patients. Impaired working memory is a major component of cognitive dysfunction in schizophrenia, as evident by diminished ability to briefly store and direct a limited amount of information to guide thought or behavior. Altered activation of dorsolateral prefrontal cortex that accompanies impaired working memory seems to be relatively specific to schizophrenia (119).

6.1. Genetics of Schizophrenia

Genetic linkage analyses reveal multiple genes conferring increased susceptibility to schizophrenia, including synapsin-2, epsin-4, neuregulin-1, dysbindin, regulator of G protein signal-4 (RGS-4), catechol-O-methyltransferase (COMT), the gamma catalytic subunit of calcineurin, and proline dehydrogenase (120). Microarray studies of schizophrenic prefrontal cortices demonstrate a selective decrease in transcripts encoding presynaptic proteins (e.g., synapsin, *N*-ethylmaleimide-sensitive factor) (121), and increased expression of apolipoprotein L1, which is a high-density lipoprotein located on a high-susceptibility locus for schizophrenia (i.e., chromosome 22q12) (122). Transgenic mice with conditioned deletion of forebrain calcineurin displayed behavioral abnormalities similar to schizophrenia (123).

One of the best-studied schizophrenia susceptibility genes is COMT, whose allelic variants encode for enzymes with different catalytic activities in the methylation of catecholamines, such as dopamine. Because dopamine transporters have low synaptic density in prefrontal cortex, COMT likely plays an important role in regulating cortical dopamine transmission. COMT-mediated methylation inhibits dopamine activity in the prefrontal cortex. Blockade of dopamine catabolism by inhibition of COMT increases prefrontal dopamine levels (124). The human Val158Met allele of COMT might increase susceptibility to schizophrenia because of its association with lower prefrontal cortical dopamine levels and less robust cognitive performance in healthy subjects (125). In animal models, COMT inhibitors increase extracellular dopamine in the prefrontal cortex and improve working memory (126). Thus, inhibition of COMT, which

results in a selective increase of dopamine in the frontal cortex without affecting subcortical regions, may represent a novel mechanism for improving cortical cognitive function in schizophrenia (127).

6.2. Neurodevelopment and Schizophrenia

There is evidence to suggest that neurodevelopmental abnormalities contribute to the pathogenesis of schizophrenia. Retrospective studies demonstrate a higher frequency of premorbid characteristics (e.g., cognitive impairment, subtle motor dysfunction, poor school performance) in healthy adolescents before the onset of a first psychotic episode (128). A greater incidence of developmental abnormalities, including aqueductal stenosis, arachnoid and septal cysts, and agenesis of the corpus callosum, are associated with schizophrenic patients (129). Functional imaging studies of schizophrenic patients reveal hypofunction in the prefrontal cortex as well as abnormal recruitment of cortical activity during performance of cognitive tasks, which might result from defects in synaptic pruning and migration of neurons (130). The thalamus is a structure that provides multiple channels of thalamo–cortical and cortico–thalamic connections as well as afferents to the amygdala, striatum, and subiculum. Functional imaging suggests that the abnormal cortico–cerebellar–thalamic–cortical circuit contributes to cognitive dysfunction (130, 131).

6.3. Dopamine-Based Antipsychotic Strategy

The role of dopamine in mediating pleasure is well established (132). The dopamine system detects novel rewards, acquires association, and directs reward-seeking behaviors (133). The dopamine system comprises a collection of neurons in the midbrain that project to the striatum (mesostriatal), limbic regions (mesolimbic), prefrontal cortex (mesocortical), and the thalamus (119). Glutamatergic cortical pyramidal neurons directly activate dopaminergic mesencephalic neurons that project to the dorsal lateral prefrontal cortex, and indirectly inhibit the mesostriatal projections.

In schizophrenia, aberrantly increased activity in the dopamine system independent of context contributes to the positive or psychotic symptoms of delusion and hallucination. Dopamine-blocking agents do not reverse the underlying etiology that produces dysfunction in the dopamine system. Thus, typical antipsychotic agents reduce the impact of psychosis, but do not take away the symptoms completely, and symptoms recur once treatment ceases (134).

The effects of dopamine are mediated by dopamine receptors, G protein-coupled receptors that are broadly divided into the D_1 receptor-like subtype (D_1R, D_5R) that activates adenylate cyclase via G_s, and the D_2 receptor-like subtype (D_2R, D_3R, D_4R) that inhibits adenylate cyclase via G_i (135). D_2 receptor occupancy is essential to antipsychotic action (136), and all typical antipsychotic agents block dopamine D_2 receptors (10). Antipsychotic efficacy is achieved when D_2 receptor blockade reaches a threshold of 60 to 70%. Greater than 80% D_2 blockade does not provide additional antipsychotic efficacy, but, instead, causes a much higher incidence of extrapyramidal side effects (134). Antipsychotic drugs are thought to block D_2 receptors in all regions where they are expressed, including the striatal, limbic, cortical, and thalamic regions, but recent data imply that there are region-specific differences in D_2 receptor blockade (137). The dose-limiting extrapyramidal symptoms likely result from blockade of mesostriatal D_2 receptors. Controversy remains whether striatal versus extrastriatal D_2 blockade or whether the two alternative splice variants (D_2 long and D_2 short) predicts antipsychotic efficacy (138). Because D_3 receptors are highly concentrated in the mesolimbic region, its blockade might produce antipsychotic effects, but the absence of D_3-selective agents have limited the development of this strategy. D_4-receptor selective blocking agents (e.g., Sonepiprazole) have not demonstrated antipsychotic efficacy in large clinical trials (10). Interestingly, D_1-receptor blockade not only lacks antipsychotic efficacy, but might even exacerbate psychotic symptoms (139).

The complex D_2 receptor-mediated intracellular signaling offers potential for novel antipsychotic therapy. D_2 receptors, through coupling to $G\alpha_i$, inhibit the cAMP-dependent signaling cascade, and, through $G\beta\gamma$ subunits, interact with different ion channels, regulate intracellular calcium stores, and activate the MAPK pathway. D_2 receptors also inhibit the activity of Akt, a serine/threonine kinase, through a β-arrestin 2-dependent and cAMP-independent mechanism (140). An important regulatory mechanism of D_2 receptor activity involves agonist-induced desensitization through phosphorylation of the receptor by G protein receptor kinase, which uncouples receptors from G protein-mediated signaling and facilitates arrestin-mediated receptor internalization (18).

6.4. Second-Generation or Atypical Antipsychotic Drugs

Atypical antipsychotic drugs are characterized by 5-HT_{2A} in addition to D_2 blocking properties and lower incidence of extrapyramidal symptoms (10, 141). 5-HT_{2A} receptors mediate aspects of the working memory (142), which is impaired in schizophrenia. Many psychedelic drugs enhance glutamatergic transmission via cortical 5-HT_{2A} receptors and produce perceptual disturbance, memory deficit, and cognitive dysfunction similar to symptoms of acute psychosis (143–146). 5-HT_{2A} receptors also facilitate dopamine release from the nucleus accumbens and the ventral tegmental area and elevate dopamine levels in the frontal cortex (147–150). Thus, 5-HT_{2A} antagonism that contributes to the therapeutic effects of atypical antipsychotics likely results, at least in part, from serotonin-mediated improvement in glutamatergic transmission and reduction in dopaminergic activity.

The oldest atypical antipsychotic drug is clozapine, which has been approved for treatment-resistant schizophrenia and is the only antipsychotic agent known to reduce suicide in schizophrenia (151). Agranulocytosis, which requires frequent blood monitoring, is a potentially life-threatening adverse effect of clozapine possibly caused by activation of H_4 histamine receptors (152). Interestingly, clozapine as well as other atypical antipsychotic drugs are clinically effective at 40% D_2 occupancy, likely because of their lower affinity. Atypical antipsychotic agents have also demonstrated clinical efficacy in bipolar disorder, anxiety disorders, and depression with psychotic features.

Aripiprazole (Abilify) is one the most recently approved antipsychotic agents. Among its complex pharmacological action, aripiprazole is a 5-HT_{2A} receptor antagonist as well as a partial agonist at the D_2, D_3, D_4, 5-HT_{2C}, and 5-HT_{1A} receptors (153, 154). Because of its D_2 partial agonism, aripiprazole achieves clinical efficacy only at D_2 occupancy greater than 85%, but it does not cause extrapyramidal symptoms. Antipsychotic strategy based solely on 5-HT_{2A}-selective blockade has largely been unsuccessful. In Phase 3 clinical trials, M100907 (a 5-HT_{2A}-selective antagonist) failed to demonstrate clinical efficacy superior to haloperidol at doses sufficient to saturate prefrontal cortical 5-HT_{2A} receptors (10, 155). At least for the short term, it would seem unlikely that a single drug would effectively improve psychotic, negative, and cognitive symptoms (10, 156).

6.5. Glutamate-Based Strategy

Dysfunction in the activation of prefrontal cortical neurons has been found in schizophrenic patients during performance of working memory tasks (157). The reduced output from prefrontal pyramidal neurons leads to a decrease in the activity of mesocortical and an increase in the activity of mesostriatal dopaminergic neurons. The NMDA glutamate receptor has multiple modulatory sites that are amenable for fine-tuning of glutamate activity, of which the glycine site is stimulatory. Glycine and D-serine are both potent co-agonists of NMDA receptors with L-glutamate. A novel antipsychotic strategy involves increasing the level of glycine or D-serine, which may enhance NMDA receptor-mediated glutamate activity (158). GLYT1 and GLYT2 are two glycine transporters that are found in both neurons and glial cells (159). Sarcosine, a naturally occurring inhibitor of GLYT1, improves antipsychotic efficacy in preliminary clinical trials as adjunctive therapy (160). In a large, multicenter, double-blind, placebo-controlled study, however, D-cycloserine and glycine did not improve cognitive or negative symptoms in schizophrenic patients (161).

7. Future Directions

Several exciting developments in neuropsychiatric research will have potentially profound impacts on the future of the field. The discovery of single-nucleotide polymorphisms (SNPs) that engenders individual variations in protein structure and function, permits us to explore how genetic susceptibility modulates the affected neural circuitry and drug-receptor occupancy in functional imaging studies as well as to predict how individuals would respond to pharmacological treatments in pharmacogenomic studies (162). Systematic comparative profiling of genes, proteins, and metabolites (e.g., health versus disease, placebo versus treatment) could further facilitate preclinical validation of drug targets as well as clinical stratification based on biomarkers that correlate with drug efficacy and toxicity (124, 163). Thus, the direction for the future will be the clinical application of individually tailored pharmacotherapy to patients suffering from neuropsychiatric disorders.

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31
Use of Laboratory Assessments in Psychiatry

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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 excluding 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 Biological effects of drugs · Laboratory use in comorbid medical conditions · Minimum laboratory tests · Therapeutic drug monitoring · Treatment adequacy · Treatment safety · Use of laboratory in psychiatry

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 and 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 excluding 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 that compliments the objective findings derived from a detailed medical history and a comprehensive physical examination. Each 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:

1.1. Clinical Vignette

Mrs. X, a 47-year-old white woman with metastatic malignant melanoma, had just completed her 4th week of adjuvant chemotherapy treatment with interferon-α. She had a history of one psychiatric hospitalization and she 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 had been making requests 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 because of increasing nausea, vomiting, diarrhea, and diffuse abdominal pain. She presented to the local emergency room (ER) 1 week later for an evaluation of persistent confusion.

Questions to consider before laboratory work-up:

- What is the working diagnosis?
- What laboratory tests might help in evaluating the diagnosis and establishing the patient's general health?

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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. Computed 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

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 the signs 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 300 mg lithium twice daily and 100 mg sertraline 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 because of agitated behavior, interpreted as a manic episode. Given this history, lithium toxicity should be considered in the differential diagnosis because 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 using stages of diagnostic sophistication presented in Table 31.2.

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,

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

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 women of childbearing potential
Vital signs

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 women of childbearing potential, especially in psychiatry, because most psychiatric medications have category C and D listings for use during pregnancy.

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 that should be considered based on the previous laboratory tests 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?

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	Gastrointestinal tract ulcer/malignancy
Urine: porphyrins, osmolality	Acute intermittent porphyria

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 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 before ordering a laboratory evaluation.

In this regard, Mrs. X was on immunosuppressant therapy and complained of nausea, vomiting, diarrhea, and abdominal pain, which can be caused by 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 UDS 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 result could be because this patient received a blood transfusion in her 20s after a motor vehicle accident. The positive UDS result could be explained by history indicating consumption of a poppy seed bagel for breakfast in addition to over-the-counter cough syrup before her admission.

Nevertheless, hepatitis panel, HIV testing, and drug of abuse confirmation tests (gas chromatography/mass spectrometry [GC/MS]) would be appropriate to further clarify the diagnosis, and determine whether an open discussion regarding illicit drug use would be appropriate (3).

5. Special Cases with Specific Laboratory Assessments

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 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.

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
Homocysteine level
Serum copper and ceruloplasmin for Wilson's disease
Urine drug screen, heavy metals screen, blood alcohol level

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 to 8 months. She also reported a family history of Alzheimer's disease 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 with 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 exclude 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 that Mrs. X reported occasional drinking with poor nutritional intake and a recent onset of nonproductive 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 older than 50 years
- Have a preexisting cardiac condition
- Are being treated with drugs known to prolong cardiac conduction (e.g., QT interval)

5.2. Substance Abuse or Dependence

Laboratory examination 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 or dependence is suspected. The most common substances of abuse or dependence detected by the UDS include cocaine, amphetamine (including ecstasy), opiates, marijuana, and benzodiazepines (3).

UDS is a screening test designed to detect a wide range of potential substances of abuse, therefore, it frequently can be falsely positive because of cross-reactivity with other chemical compounds. Several medications, such as bupropion and OTC Vicks® inhaler can produce false positive test results for amphetamines; poppy seeds and some antibiotics (levofloxacin, ofloxacin) can cause false positive test results for opiates; and diphenhydramine for tricyclics. A false positive UDS result for the presence of drugs of abuse could result in unnecessary confrontation. In those cases in which patients deny the use of illicit drugs despite a positive UDS, a confirmation test by 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. Because each laboratory is set up to detect certain levels of the questioned compound with preset threshold for each substance of interest, 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 a dental procedure, which, by itself, is rarely sufficient to produce a positive UDS result.

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 support and intensive outpatient chemical dependency treatment before initiation of interferon treatment. Her serum gamma glutamyl transferase (SGGT) and carbohydrate-deficient transferrin (CDT) results were within normal limits.

6. Neuroimaging

Recent advances in these procedures permit assessment of both structural and functional abnormalities in the brain.

Computed tomography (CT) (10) is widely used in the ERs and is especially indicated for patients presenting with psychiatric symptoms if they belong to one of the categories described below:

- Older than 40 years with no psychiatric history
- First episode of psychosis, mania, or acute personality change
- Differential diagnosis of delirium or dementia
- Rapid onset of neuropsychiatric symptoms
- Abnormal neurological examination
- Recent memory loss

A CT scan of the head is used primarily to exclude hemorrhagic insult to the brain or space-occupying lesion. Lumbar

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 levels 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, and folate levels; 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.

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 the orbital medial prefrontal complex, amygdala, striatum, and thalamus (11–13). Magnetic resonance imaging (MRI), functional MRI (fMRI) (14), and magnetic resonance spectroscopy (MRS) have the advantages of assessing both brain structural and functional status by using noninvasive 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, CT scanning was used during her ER visit to exclude 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.

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,	Periodic complexes
Creutzfeldt–Jakob disease	Periodic complexes

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: Clinical response = Site of action × Drug concentration at site of action × Biology of patient (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).

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 that have a narrow therapeutic index.

TDM can vary in terms of usefulness with a drug from necessary to simply helpful. 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

TABLE 31.8. Clinical response formula.

Clinical response		
Site of action	Drug concentration at site of action	Underlying biology of patient
Affinity for site Intrinsic activity at site	**A**bsorption **D**istribution **M**etabolism **E**limination	**G**enetics **A**ge **D**isease **E**nvironment

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 Sertraline: 10–50 ng/ml on 50 mg/day Paroxetine: 70–120 ng/ml on 20 mg/day Fluoxetine and norfluoxetine: 120–300 ng/ml on 20 mg/day Citalopram: 85 ng/ml on 40 mg/day Fluvoxamine: 100 ng/ml on 150 mg/day	No need for routine TDM Useful for individual dose optimization Determination of the medication presence
Bupropion	Risk of seizures above 450 mg/day Incidence of seizures is dose dependent Effect caused by 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	Not used routinely because of limited data Might be useful because of increased risk of seizures and lower efficacy at higher plasma levels Useful in preventing drug to drug interactions and safety
Venlafaxine	Linear pharmacokinetics Ascending dose–response relationship	Optimal plasma concentration: 195–400 ng/ml at a dose of 75–375 mg/day 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-HTT receptor occupancy	Not used routinely because of wide safety margin
Nefazodone Trazodone	Nefazodone: nonlinear kinetics, hepatotoxicity	No optimal level range	Not established
Mirtazapine	Linear pharmacokinetics Multiple metabolites	Broad therapeutic index	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 caused by extensive metabolism by CYP enzymes Difficulty detecting early development of toxicity Delayed onset of action	Threshold therapeutic plasma level: 350–450 ng/ml	Is important in assessing efficacy and safety
Risperidone	Higher levels have been reported to be associated with poorer clinical response and possibility of higher extrapyramidal side effects	Expected ranges are not readily available for use in clinical practice. Instead, dopamine D2 receptor occupancy might have implications for the magnitude of clinical response (37)	Can be considered
Olanzapine	Dose–response correlation	Level greater than 23.2 ng/ml for olanzapine was associated with improved clinical response (38)	Not established
Quetiapine, ziprasidone, aripiprazole	Dose–response correlation	Expected ranges are not clinically established	Not established

MAO, monoamine oxidase; NE, norepinephrine; DDI, Drug-drug interaction

TDM with antidepressant (21, 22) and antipsychotic medications (Table 31.9) can be beneficial when the patient:

- Is taking a tricyclic antidepressant (23)
- Is experiencing an acute and serious medical illness
- Is 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, sex, 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 nonsmokers (Table 31.10). Conversely, higher plasma concentrations have been documented in women, perhaps because of a higher volume of distribution associated with increased body fat in women versus men and in patients between the ages of 45 and 54 years. Inhibition of CYP1A2 could instead lead to higher clozapine concentrations in cases 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 and 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 because clozapine is used preferentially in individuals with treatment-refractory schizophrenia and severe psychotic illness. The loss of efficacy can lead the patient to become of danger to self or others (24–26).

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 nonresponders because of inadequate plasma levels of the drug.

Editor's Note: Polymorphism tests for cytochrome P450 system isoforms are currently used to determine whether an individual would be a rapid or slow metabolizer, which, in turn, would provide crucial information when selecting a psychotropic medication. For example, genotyping assays for CYP2C19 and CYP2D6 are currently available for the determination of such polymorphisms. The CYP2D6 and CYP2C19 genotyping assays are included in the treatment-resistant depression panel to aid in selecting a proper antidepressant.

7.1. Mood-Stabilizing Drugs

Returning to the case of Mrs. X, she 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 the 0.8 to 1.0 mEq/L range. She did not experience any adverse effects until recently, when she decided to stop taking all of her medications because of difficulty swallowing. She presented for an evaluation to the local ER 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,

TABLE 31.10. Monitoring physiological effects of clozapine.

Laboratory test	Baseline	Follow-up	Drug effect
Complete blood count (CBC) with differential white blood cell (WBC) and agranulocyte (ANC) count	WBC $\geq$ 3,500	Initially weekly	Agranulocytosis
	WBC $\geq$ 2,000	After 6 months, biweekly After 1 year, monthly	ANC <500 cells/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 levels return to normal	Stop clozapine, initiate reverse isolation, do not rechallenge
Seizures	Obtain history	Seizure risk: • <300 mg daily: 1–2% • 300–600 mg daily: 3–4% • >600 mg daily: 5%	Black box warning regarding dose-dependent risk of seizures
Liver function tests	X	As clinically indicated	Cholestatic jaundice. Increased liver enzymes.
ECG	In patients with preexisting cardiac disease	As clinically indicated	Hypotension Tachycardia Myocarditis
Clozapine level	After treatment initiation or dose adjustment	Therapeutic level:350 to 450 ng/ml(clozapine and norclozapine)	Clinical effect is influenced by multiple variables: dose, sex, smoking, age, body weight, caffeine intake, and drug–drug interactions

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 1 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 caused by lower urinary citrate excretion and increase in urinary pH.

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 the 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 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 according to the recommendation of the American Diabetes Association Consensus Panel (28, 29) (Table 31.14); personal and family medical history at the beginning of

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	XX [a]	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 [a]	Every 6–12 mo	Hypothyroidism
Electrocardiogram	In patients older than 40 years 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 mo 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

[a] Expanded test might be needed if clinically indicated.
BUN, blood urea nitrogen.

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 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 Metabolic 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 adjustment12 hours after the last dose	Every 6–12 months, as indicated	Serum level: 50–125 μg/mL

SGOT, serum glutamic–oxaloacetic transaminase; SGPT, serum glutamic–pyruvic transaminase; LDH, lactate dehydrogenase.
*Editor's comments: weight and BMI should be checked each visit; measurements of serum lipids, Hemoglobin AIC, should be checked every 6–12 months.

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[a] Thrombocytopenia
Pregnancy test	X	Document contraceptive method because the effectiveness of oral contraceptives can be compromised	Craniofacial defects. Spina bifida Developmental delay
Liver function tests	X	Every 6–12 months	Hepatotoxicity Transient increase in SGOT, SGPT, alkaline phosphatase Hepatitis Cholestatic jaundice
ECG	In patients with preexisting 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 antidiuretichormone syndrome
Carbamazepine level	After 5 days of initial dose or dose adjustment12 hours after the last dose	Weekly for the first 2 months, then biweekly for another 2 months	Serum level: 8–12 μg/mL[b]

Document the contraceptive method. SGOT, serum glutamic–oxaloacetic transaminase; SGPT, serum glutamic–pyruvic transaminase.
[a] Carbamazepine is contraindicated in patients with a history of bone marrow suppression. Carbamazepine should be discontinued if WBC $< 3{,}000$ cells/mm^3, absolute neutrophil count $<1{,}500$ cells/mm^3, or platelet count $<100{,}000$ cells/mm^3.
[b] Carbamazepine induces its own metabolism, leading to a decrease in serum level.

TABLE 31.14. ADA consensus on antipsychotic drugs, obesity, and diabetes: monitoring protocol.

Start	Start	4 Weeks	8 Weeks	12 Weeks	6 Months	12 Months	5 Years
Personal/family history	X					X	
Weight (BMI)	X	X	X	X	X	X	X*
Waist circumference	X					X	X
Blood pressure	X			X		X	X
Fasting glucose HgA1C	X			X		X	X
Fasting lipid profile	X			X	X	X	X

Clinical status may warrant more frequent assessments. BMI, body mass index.
Adapted with permission from the American Diabetes Association (39).
*Editor's comments

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 them an outlier on the usual dose–response curve for a drug.

Numerous studies advocate for and against extensive laboratory testing. The bottom line is that 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 ER physicians seem to be in agreement with psychiatrists by frequently ordering the same tests (6, 8, 33). Routine UDS did not seem 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 because 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 using 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 ranges, 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 31.15. ADA consensus on antipsychotic drugs, obesity, and diabetes.

Drug	Weight gain	Diabetes risk	Dyslipidemia
Clozapine	+++	+	+
Olanzapine	+++	+	+
Risperidone	++	D	D
Quetiapine	++	D	D
Aripiprazole[a]	±	–	–
Ziprasidone[a]	±	–	–

[a] Newer drugs with limited long-term data.

+, Increased effect; –, no effect; D, discrepant results.

Adapted with permission from the American Diabetes Association (39).

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Epidemiology of Psychiatric Illness

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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 bases for more extensive studies of etiology.

Keywords Comorbidity · Epidemiology · Etiology · Incidence studies · Prevalence studies

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 the elderly. 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 recently 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 (4–8).

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 people with a given risk

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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. Because of the current state of knowledge regarding risk factors in psychiatry, the use of this experimental approach has, for the most part, been limited to clinical therapeutic trials. However, psychiatric epidemiologists have capitalized on naturally occurring quasi-experimental situations, such as disasters 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 (9), to identify ethnic disparities in unmet need (10), and to identify predictors of type of help used (11). Studies such as these have been used to develop more effective and efficient approaches to the delivery of mental health services.

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.

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.

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. In terms of case ascertainment, 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 the elderly). Although attempts have been made to establish more comprehensive sources of treatment data through the use of psychiatric case registers covering all mental health providers in a geographically defined area, the use of these data will seriously underestimate the numerator of incidence and prevalence rates in ways that are not uniformly distributed across different population subgroups.

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. 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 people 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 (e.g., SUDAAN) (12). 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.

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, because 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. Thus, surveys with response rates less than 70% are generally considered potentially biased toward underestimation of true prevalence.

2.1.3. Time Perspective

In general, for episodic conditions, such as episodes of major depression, prevalence equals incidence times 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 (13).

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 United States 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 (14).

In contrast, after World War II, in the predominant psychiatric epidemiologic studies in the United States, 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 (15). 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) (16). 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 (15), 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 United States (where schizophrenia was approximately one third more prevalent) and the United Kingdom (where the prevalence of mood disorders was several times greater) led to a series of studies (17, 18) 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 United States, the first published, specified criteria for a subset of mental disorders were the Feighner criteria (19). Subsequently, a set of Research Diagnostic Criteria (RDC) was developed (20). These developments provided impetus for a third revision of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-III) (21) of the American Psychiatric Association, which became the official US psychiatric nosology in 1980, the most recent revision of which, DSM-IV-TR, was published in 2000 (22).

The impact of these diagnostic developments on psychiatric epidemiology in the United States 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 people with no diagnosable psychiatric disorder will also score in the “case” range. Dohrenwend et al. (23) 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 (24). 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 United States that applied these specified diagnostic criteria to a community sample was a pilot study of 500 people carried out by Weissman and colleagues (25) 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 (26). 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 (26). 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 United States, the National Comorbidity Survey (NCS) was conducted in the 1990s, the first study of the prevalence of psychiatric disorders in community-dwelling adults, aged 15 to 54 years, using a nationally representative sample (5). The NCS used a semistructured interview, the Composite International Diagnostic Interview (CIDI) (27). 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 recently used in the World Health Organisation (WHO) World Mental Health Surveys (MHS) (7).

It is important to note that psychiatric disorders are currently defined in the nomenclature by their symptom presentation, but current research is exploring the role of genetic factors and biological risk factors, such as neuroimaging data (e.g., lesion size and proportions).

2.3. Reliability and Validity of Diagnostic Instruments

Even given the availability of valid diagnostic criteria such as those provided by DSM-IV-R, 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 caused by inconsistencies in measurement (28). 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 administration, 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.

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, because 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, whereas 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 (26). Most earlier studies demonstrated evidence of satisfactory reliability with little attention to validity issues.

3. Descriptive Epidemiology: Prevalence Studies

Before the publication of DSM-III (21), 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 (29) was the first large-scale study of the prevalence and incidence of psychiatric disorders in community and institutional populations. As previously mentioned, the surveys were conducted using representative samples in five US cities in the late 1970s and early 1980s: New Haven; Baltimore; St. Louis; Durham, NC; and Los Angeles. The target population was all adults 18 years or older living in a designated mental health catchment area, and the sampling frame included residents of both households and institutions. The ECA used the DIS (26) to obtain information on a series of symptoms, which could then be mapped to DSM-III, and used to generate diagnoses. A staff of rigorously trained field interviewers administered the DIS at each of the sites, and, through a series of structured probes, psychiatric symptoms caused by medical illness and medication, drugs, or alcohol were eliminated. Results of the ECA surveys have been documented in detail (13), and this survey remains the landmark study with which other estimates are compared. Prevalence estimates for community residents are reported in Table 32.1. Participants in the ECA were re-interviewed using the DIS 12 months after the baseline interview.

Other large-scale epidemiologic studies using the DIS followed. One example is a population-based study of 3,258 adults 18 years 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 (30).

The NCS was conducted in the 1990s using a stratified, multistaged probability sample of all adults in the United States aged 15 to 54 years (5). A total of 8,098 respondents were interviewed. Psychiatric diagnoses were based on DSM-III-R (31) criteria, which were in place at the time of the survey. The diagnostic instrument used in the NCS was a modified version of the CIDI (27), a structured instrument based on the DIS. 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 non-institutionalized Dutch adults aged 18 to 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 below.

The WHO World MHS were recently conducted in 14 countries (7), and diagnoses were based on DSM-IV criteria (32). In the United States, the survey was called the NCS Replication (NCS-R) (33). 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 MHS sites, Mexico, Europe, and China. In the Mexican NCS (M-NCS), a representative sample of 5,826 adults, aged 18 to 65 years, participated (34). 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 (35). The World MHS was also conducted in two areas of China (C-MHS): Beijing (B-MHS) and Shanghai (S-MHS). A total of 5,201 adults 18 years or older were interviewed from a representative probability sample of those two areas. Prevalence estimates are provided in Table 32.1.

The National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) baseline survey was recently conducted in the United States (8). A total of 43,093 adults 18 years or older were selected through a representative sample of the US adult population. The diagnostic instrument used in this survey was the Alcohol Use Disorder and Associated Disabilities Interview—DSM-IV Version

TABLE 32.1. Prevalence of psychiatric disorders in selected community-based studies.

Selected disorders	ECA		NCS		NEMESIS			NCS-R		M-NCS	ESEMeD		C-MHS	NESARC
	LT	1 Month	LT	12 Months	LT	12 Months	1 Month	LT	12 Months	12 Months	LT	12 Months	12 Months	LT
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	
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	
Alcohol abuse or dependence	13.3	2.8								2.2	5.2	1.0	1.6	
Drug abuse or 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
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
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
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
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	
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	
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
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
Posttraumatic stress disorder								6.8	3.5	0.6	1.9	0.9	0.2	
Obsessive–compulsive disorder	2.5	1.3			0.9	0.5	0.3	1.6	1.0					
Severe cognitive impairment	1.3	1.3												

ECA, Epidemiologic Catchment Area Surveys, 5 US sites, 18,571 adults 18 years and older, DIS (DSM-III) (4); NCS, National Comorbidity Survey, representative sample in the United States; adults 15 to 54 years old, CIDI (DSM-III-R) (5); NEMESIS, Netherlands Mental Health Survey and Incidence Study, representative sample in the Netherlands, 7,076 adults 18 to 64 years old, CIDI (DSM-III-R) (6,39); NCS-R, National Comorbidity Survey Replication (part of the WHO World Mental Health Survey), representative US sample, 9,282 adults 18 years and older, CIDI (DSM-IV) (33,37); M-NCS, Mexico National Comorbidity Survey (part of the WHO World Mental Health Survey), representative sample; adults 18 to 65 years old, CIDI (DSM-IV) (34); ESEMeD, European Study of the Epidemiology of Mental Disorders (part of the WHO World Mental Health Survey), 21,425 adults 18 years and older, CIDI (DSM-IV) (35); C-MHS, Chinese World Mental Health Survey (part of the WHO World Mental Health Survey), 5,201 adults 18 to 70 years old in Beijing and Shanghai, CIDI (DSM-IV) (38); NESARC, National Epidemiologic Survey on Alcohol and Related Conditions, representative US sample, adults 18 years and older, AUDADIS-IV (DSM-IV) (8); LT, lifetime.

(AUDADIS-IV) (36). Prevalence estimates of selected disorders are provided below.

Table 32.1 presents the prevalence estimates for eight large-scale psychiatric epidemiologic studies discussed above. Overall, the prevalence estimates are fairly consistent, but differences are also noted. In comparing the prevalences 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 recently conducted NCS-R, which includes adults across all age groups, the lifetime prevalence of any DSM-IV disorder was 46.4% (37). 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%) (33). A similar pattern was observed in the other MHS components (34, 35, 38).

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.

3.1.1. Age

The 1-month prevalence of any psychiatric disorder from the ECA study was 16.9% among those aged 18 to 24 years, 17.3% among those aged 25 to 44 years, 13.3% among those aged 45 to 64 years, and 12.3% among those 65 years or older (4). Among those aged 18 to 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 to 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 to 64 years, the most prevalent disorders were phobic disorder (6.0%) and dysthymia (3.8%). Among those older than 65 years, 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 with people 45 to 54 years old (the oldest age group in this sample), the odds of any disorder were increased for those 35 to 44 years old (odds ratio [OR] = 1.24), those 25 to 34 years old (OR = 1.51), and for those 15 to 24 years old (OR = 2.06) (5). That is, compared with those 45 to 54 years old, the probability of having a psychiatric disorder was 1.24 times higher among those 35 to 44 years old, 1.51 times higher among those 25 to 34 years old, and 2.06 times higher among those 15 to 24 years. A similar pattern was observed in NEMESIS, in which the prevalence of one or more disorders in the past 12 months was 14.9% among those 55 to 64 years old and 33.8% among those 18 to 24 years old (39). Significant differences by age were also reported in the ESEMeD project, in which the 12-month prevalence of any mental disorder was 13.7% among those 18 to 24 years old and 5.8% among those 65 or older (35). 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 18 to 34 years old (7, 34, 38).

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 with men (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 (39). 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 (38). 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 (34).

3.1.3. Race

The ECA data (13) 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, sex, marital status, and socioeconomic status, there were virtually no significant differences in ethnicity by specific diagnostic categories.

In the NCS, blacks were less likely than whites were to have any 12-month psychiatric disorder (OR = 0.70). Hispanics were more likely than whites were 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 were (OR = 0.47). Hispanics were 1.86 times more likely to have three or more comorbid disorders in the past 12 months compared with whites (5).

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 are 1.8% for alcohol abuse or dependence, 1.1% for substance abuse or dependence, 1.6% for major depression, and 4% for phobias (40, 41). Estimates from the NEMESIS were generally higher (42), 2% for alcohol abuse and 3.1% for major depression. In Edmonton, the annual incidence of alcohol dependence was 4.48% in males and 1.2% in females. The incidence of major depression was 1.96% in males and 3.72% in females (43). 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. (40) 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.

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 more than 50%, with four categories (somatization, antisocial personality disorder, panic disorder, and schizophrenia/schizophreniform) having more than 90% comorbidity (13). The strongest statistical associations included schizophrenia with mania and panic disorder; depression with mania, panic disorder, and somatoform disorder; mania with panic disorder, obsessive–compulsive disorder and antisocial personality disorder with alcohol and drug abuse or dependence. Robins et al. (13) 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 that 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 (33).

In the NEMESIS, 4.4% meet criteria for two or more disorders in the previous 12 months (39). 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 (38), findings similar to those reported from the NCS.

6. Use of Mental Health Services

In the ECA data, relatively few people 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 (13). In the recently conducted WHO World MHS, disorder severity was correlated with probability of treatment. However, in developed countries, 35.5 to 50.3% of serious cases received no treatment in the 12 months before the interview. The percentage is much higher in countries that are less developed (76.3–85.4%). In the United States, 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 show a consistent pattern during the last 20 years, that a significant number of people in the community with a psychiatric disorder do not receive treatment.

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 present examples of biologic, 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. Given the plethora of studies emerging in the literature, any comprehensive model today could potentially limit our inquiries, because many factors may be discovered in the future (such as interactions between social and genetic 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 with men and the lower frequency of major depression among community dwelling elders compared with 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.

7.1. Biological Origins

Studies of biologic origins of psychiatric disorders substantiated by community-based epidemiologic studies may be simply divided into two 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 somatic symptoms (44).

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 with 4% in dizygotic twins (45). 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 (46).

The second broad category consists of those studies that identify potential external biologic 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 to 1945 (47). 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 least twofold. Such studies, however, are only suggestive. Except for twin studies, exploration of biologic causation of

psychiatric disorder, especially external causation (such as exposure to toxins) is in its infancy.

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 is a construct that is rarely applied in North America. 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 (48, 49).

Temperament, another psychological construct, has been associated with the onset of psychiatric disorders. Modern 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 (50).

Cognitive distortions, a third psychological construct, have been proposed by Beck (51) as a cause of depression across the life cycle. In theory, the depressed person 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 (52).

7.3. Social Origins

By far, the most extensive evidence for the etiology of psychiatric disorders substantiated by epidemiologic studies supports social factors as risks for psychiatric illness. 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 be either 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.

In a recent study, the continuous stress of deployment to Iraq among soldiers was associated with neuropsychological symptoms (53) including confusion, difficulty maintaining attention, verbal learning, and visual–spatial memory. In another study, deployment was associated with an increased risk for DSM-IV psychiatric disorders including major depression and posttraumatic stress disorder (54). 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 (55). 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) (56, 57). 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 studies demonstrating the association are briefly reviewed. 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 is poorly understood.

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. Parental loss through death or separation has been associated with depression, agoraphobia with panic attacks, and generalized anxiety disorder (58). Studies, however, have not been uniformly supportive of this association. Nevertheless, recent studies have suggested that childhood trauma may be associated with neuropathological findings that are known to be associated with psychiatric disorders, such as hippocampal damage (59, 60). 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 (61). Sexual assault has been found to increase the risk of major depression as well as alcohol and drug abuse, up to threefold (62).

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 (63).

7.3.2. Socioeconomic Status

Low social economic status using indices of education, occupation and income, have long been associated with psychiatric disorders (64, 65). Community-based studies of use of mental health services by the severely and chronically mentally ill have 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 caused by low socioeconomic status. For example, the discrepancy between socioeconomic status and schizophrenia may largely be a phenomenon of large cities (66). The second theory suggests that socioeconomic status does not necessarily cause schizophrenia but rather that schizophrenia and its debilitating effects on social function lead to downward mobility in socioeconomic status (67). 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 (33). These investigators did find, however, that less than a high school education was associated with an increased frequency of some disorders.

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 (13). 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 addition, epidemiologic studies have shown a consistent association between work-related stress and psychiatric disorders (although this literature is limited) (68). For example, in Norway, physicians have higher suicide rates than the general population (69).

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%) (70). 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 approximately four times higher among individuals who have never married when compared with the married (71). This finding, however, is probably because of the early onset of schizophrenia, which decreases the likelihood of marriage.

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 (72). The strongest association between impaired social support and psychiatric disorders, especially depression, has been found with perception of support. For example, in a recent 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) (73). Social support can mediate between these factors and the onset of psychiatric disorders. In one study, perceived social support was used to mediate the association between disability and depressive symptoms over time among older adults (74). 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 (75).

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 (76). 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 (77). Small rural communities were postulated to be more integrated and, therefore, protective against the onset of psychiatric disorders. Findings from the recent NCS-R confirmed the slight increased risk of psychiatric disorders in urban compared with rural settings for more severe psychiatric disorders (33).

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33
Suicide and Attempted Suicide

J. John Mann, MD and Dianne Currier, PhD

Abstract An estimated 877,000 lives were lost through suicide worldwide in 2002. In the United States, in 2003, more than 31,000 individuals died by suicide, making it the 11th 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. More than 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 definite plan for 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 Attempted suicide · Major depression · Prevention · Risk factors · Suicide

1. Suicide and Attempted Suicide

1.1. Demographics

Worldwide, in 2002, an estimated 877,000 lives were lost through suicide, representing 1.5% of the global burden of disease and accounting for 20,767,000 Disability Adjusted Life Years (years of healthy life lost through premature death or disability) (1). In the United States, in 2003, suicide was the 11th leading cause of death, and accounted for 31,684 deaths, a rate of 10.8/100,000 (2). From 1990 to 2000, the overall suicide rate declined from 12.4/100,000 to 10.7/100,000 (3). However, suicide remains the third leading cause of death in the 15- to 24-year age group despite a 21% decline from 1990 to 2000 (13.2 down to 10.41/100,000) (2). Disproportionally high suicide rates are also found among males older than the age of 65 years (4). In the United States, men die by suicide more than four times more frequently than women (men 17.6 versus women 4.3/100,000 in 2003), and white Americans are more than twice as likely to die by suicide than African Americans and all other racial groups combined (12.1, 5.1, and 5.5/100,000, respectively, in 2003) (2). Table 33.1 shows suicide rates by sex and age group for the United States in 2002.

Suicides may be underreported or underestimated because of medical examiner or coroner experience and practice, and social factors such as stigma. Opinions differ regarding the magnitude of the underestimation, ranging from 10 to 50% (5). Most of the missed cases of suicide are reported in the category of cause undetermined. Holding and Barraclough found evidence that missed cases are descriptively more like suicides than like accident victims (6). 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 to 25 suicide attempts for each suicide. Kessler et al., using US national epidemiological

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TABLE 33.1. 2002 United States suicide rates per 100,000 population by age group and sex.

	Total	Males	Females
All ages	10.8	17.6	4.2
15–24 years	9.7	15.9	3.3
25–44 years	13.9	21.9	5.7
45–64 years	15.0	23.5	6.9
65 years and older	14.6	29.8	3.79

Center for Disease Control (2).

data, estimated that there are approximately 500/100,000 suicide attempts per year, which is a ratio of approximately 50:1 attempts to suicides (7). 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 older than 65 years of age only 4:1 (8, 9). Women report attempting suicide approximately three times as often as men (10).

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 (11)

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 suicide (12–15). 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 completed suicide, whereas women tend to use less lethal suicide methods with a higher chance of survival (11). Thus, differences in 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. Kessler et al., in an epidemiological study in the United States, estimated the rate of suicidal ideation at 2.8 to 3.3% of the general population (7), and Weissman et al., reported between 2 and 18% across nine countries (10).

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, and may also have genetic and biological dimensions (16, 17).

2. Neurobiology of Suicidal Behavior

Impairment in a number of neurobiological systems has been associated with suicide and/or attempted suicide. Observed changes in neurobiological systems may be associated with a primary psychiatric disorder, 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, 2003 (18) for a review). Serotonin impairment associated with suicidal behavior seems to be a trait and, hence, can predict future behavior and correlates with lethality of past suicidal behavior (19, 20). A meta-analysis of prospective studies of 5-HIAA, the 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 those with low CSF 5-HIAA had a more than fourfold risk chance of dying by suicide (21). 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. Postmortem studies of the brains of those who died by suicide have localized abnormal serotonergic function to the ventromedial prefrontal cortex (22–24), a region of the brain involved in the executive function of behavioral and cognitive inhibition (25), 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 (26) and impulsivity (27). In depressed suicide attempters, lower CSF

5-HIAA levels are associated with greater aggression and hostility. Interestingly, among suicide attempters, only those who make more highly lethal attempts have a lower CSF 5-HIAA level, indicating a serotonin deficit comparable to completed suicides, whereas low lethality attempters have CSF 5-HIAA levels comparable to non-attempters (14, 28).

Abnormalities in the noradrenergic system and the hypothalamic–pituitary–adrenal (HPA) axis have also been associated with suicidal behavior (for a review, see Mann, 2003 (18)). Both systems are related to stress response, and dysfunction in these systems seems to be state dependent rather than a correlate of enduring traits of the diathesis. There are fewer noradrenergic neurons in the rostral or upper locus ceruleus 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 (29). There are also indications of cortical noradrenergic overactivity, such as presence of lower alpha and high-affinity beta$_1$-adrenergic receptor binding sites in cortex of suicide victims (30).

Suicidal patients in diagnostically heterogeneous populations exhibit HPA axis abnormalities, most commonly, resistance to dexamethasone challenge (31–39). A meta-analysis of prospective studies of HPA axis dysfunction and suicide reported a 4.65 increase in risk for dexamethasone nonsuppressors (21).

Other biological systems being investigated with respect to suicidal behavior include fatty acids (40), cholesterol (41), and neurotrophic factors, such as brain-derived neurotrophic factor (BDNF) (42).

3. Heritability of Suicidal Behavior

Suicide and nonfatal suicide attempts cluster in families of individuals who commit suicide or make suicide attempts (43–47). This is the case in comparison with both general population control subjects and with psychiatric control subjects who have never attempted suicide. A meta-analysis of 22 controlled family studies covering both suicide attempts and suicide found a nearly threefold overall increased risk of suicidal behavior among close relatives of suicidal versus nonsuicidal individuals (48). Suicidal behavior is transmitted in families, in part, independently of the transmission of mood disorders and other major psychiatric syndromes (49).

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 current stressors. Evidence of a genetic contribution comes from twin studies, which have shown a higher concordance rate for both suicide (50) and suicide attempts (51) in monozygotic versus dizygotic twins. Pooled data from seven twin studies found that the overall concordance for suicide or suicide attempt was 23.5% in MZ twin pairs versus 0.13% in DZ twins (48). Twin studies indicate that genetic factors predict 17 to 45% of the variance in suicidal behavior (52, 53), and individual and shared environmental influences together accounted for 35 to 75% of the variance (54). 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 die by suicide compared with biological relatives of nonsuicidal adoptees (55). There is more than a 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 because of the variability of lethality and intent of suicide attempts affecting degree of genetic effect (56). A large Australian twin study found a genetic contribution to suicide attempts and even suicidal ideation (52). In general, the heritability of suicide is comparable to the heritability of other major psychiatric disorders, such as bipolar disorder and schizophrenia (52).

3.1. Pathways for the Family Transmission of Suicidal Behavior

Family (57) and twin (52) studies find little evidence that imitation or modeling play a measurable role in the familial transmission of suicidal behavior. Rather, a combination of genetic and environmental factors influencing 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 5HT1A, 5HT1B and 5HT2A receptors, monoamine oxidase A (MAOA; an enzyme responsible for the degradation of serotonin), and tryptophan hydroxylase 1 and 2 (TPH1, TPH2; the rate limiting biosynthetic enzyme for serotonin) (see Mann, 2003 (58) for a review).

These genetic studies have mostly been association rather than linkage studies and have produced inconsistent results (see Baldessarini and Hennen, 2004 (48) for a review). A meta-analysis of 14 serotonin 5HT2A 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 promotor (5-HTTLPR) and suicide, but no such association for a 5HT2A receptor 102T/C polymorphism (59). 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 (58) for a review). The TPH1 gene expresses a form of TPH found in the pineal gland and outside the brain. TPH2, a more recently discovered gene, is expressed in the brain; and preliminary studies link an intronic polymorphism to

completed suicide and depression (60). Other genetic studies investigate associations between genes and behavioral phenotypes related to suicidal behavior, such as aggression and impulsivity (see Courtet, 2005 (61) for a review). Promising associations have been found for a functional MAOA gene promotor variant (MAOP) and violent and impulsive behavior, particularly in men (61, 62). Suicide and suicide attempt are complex behaviors and likely to be polygenically determined phenomena. Emerging genetic research techniques such as microarrays and single nucleotide polymorphism (SNP) chips evaluate association of thousands of genes with disease and may further identify relevant genes.

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 men but not women (63, 64). Caspi et al. found that the lower-expressing allele of the serotonin transporter gene was associated with increased risk for both depression and suicidality in response to stressful life events (65).

4. Risk Factors for Suicidal Behavior

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 that of 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 (66). Diagnosis by psychological autopsy has proven to be reliable and valid (67). To avoid selection bias, it is best to study a consecutive and, therefore, unselected series of cases, although psychological autopsy studies that investigate clinical and other factors beyond diagnosis often adopt a case–control approach.

More than 150 psychological autopsy studies have been conducted since the early 1960s, a review of which reported rates of psychiatric disorder in suicides as 91% (ranging from 23–100%) in case series reports, and 90% (ranging from 86–97%) in case–control studies (68). 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, pathological gambling or Axis II disorders, or symptoms and signs may be subthreshold (69). Most studies find approximately 90% of suicides have a diagnosable psychiatric disorder (68), although there are exceptions to these findings, for example, in a Chinese psychological autopsy study, 37% of suicides had no psychiatric disorder (70). This high number was largely caused by 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 in a consecutive series, or as 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) that measures the increase in rate in death by suicide in a certain population, for example, individuals with a mood disorder, compared with 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.

4.1.1. Mood Disorders

Mood disorders (major depressive disorder [MDD] and bipolar I and II disorders), are the most frequently found disorders in psychological autopsy studies of suicide. Reported rates range from 30 to 93% in case series studies, and 23 to 95% in case–control studies (68). Meta-analyses pooling results of individual studies report that a mood disorder diagnosis is found in 30 to 60% of suicides (68, 71, 72).

Studies of hospitalized cohorts give the rate of suicide in mood disorders as 4 to 13%, whereas community samples report lower rates, 2.7% to only slightly higher than general population levels (see Angst, 2002 (73)). 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- to 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 (73).

There is some debate regarding the relative levels of risk for suicide in bipolar disorder and MDD. In a review of 30 bipolar disorder studies, Goodwin and Jamison found that 18.8% of all deaths were by suicide. Although this rate is higher than the widely cited rate of 7.7% for MDD (74), 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 follow-up calculated SMRs of approximately 20 for MDD and

15 for bipolar disorder (75). More recent large record-based follow-up studies of hospitalized mood disorder patients also report higher SMRs for MDD than bipolar patients (73, 76).

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 (77). However, others found no difference in the SMR for suicide between bipolar I and bipolar II disorder (11.53 and 14.15, respectively) (73). The depressive phase of bipolar disorder seems 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 in mania (78–81).

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 attempt were 29.2% in bipolar and 15.9% in MDD. A community study of 1,709 adolescents followed until age 30 years documented the rate of suicide attempt in bipolar disorder at 44.4% compared with 22% in MDD (82). Both case series and epidemiological studies report the highest suicide attempt rate in bipolar II disorder (24–34%), the lowest in MDD (12–16%), with bipolar I disorder intermediate (17–24%) (83).

4.1.2. Psychotic Disorders

Meta-analysis of 38 reports with a combined population of 30,000 schizophrenic patients found an 8.5-fold greater risk of dying by suicide in schizophrenic patients compared with the general population (75). Two recent reevaluations of the literature reporting suicide rates in schizophrenic patients find that 4 to 5.6% of schizophrenic patients die by suicide (84,85), a lower figure than the commonly cited 10 to 13% (86, 87). Psychological autopsies report that 14.1% of suicides have a diagnoses of schizophrenia (19.9% in clinical populations, and 7.5% in the general population) (71). Schizophrenia has a higher representation in studies of clinical populations than in community samples (88), because 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 (89–92), as is substance use disorder (93). Approximately 20 to 50% of schizophrenic patients report making a suicide attempt (94, 95).

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 (1986) reported seven instances of schizoaffective disorder (3%) under the rubric of "other psychoses" (96), Arato et al. (1988) made the diagnosis twice (1%) (97), and Asgard (1990) found it in 11 cases, considering it the primary diagnosis in 2 cases (2%) (98). 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 (71).

4.1.3. Personality Disorders

Personality disorders have come under increasing scrutiny with respect to suicidal behavior. Meta-analysis of psychological autopsies reports 13 to 16% of cases diagnosed with personality disorders (71, 72). Personality disorders are frequently comorbid with other psychiatric disorders, and mortality figures for personality disorders do not always indicate whether another disorder was present, thus, it is difficult to ascertain the suicide mortality rate for personality disorder alone. One meta-analysis reported that, in suicides in the general population, 3.2% had personality disorder as the only diagnosis, but the rate rose to 13% and when personality disorder was comorbid with another diagnosis (71). Suicidal behavior in personality disorders is often in context of comorbid major depression and/or alcohol and substance use disorders (99–101). Nevertheless, a personality disorder diagnosis confers a sevenfold increase in risk for suicide (75). Suicide attempt rates are strikingly elevated in some personality disorders, particularly the impulsive/aggressive Cluster B disorders, such as borderline personality disorder, in which suicide attempt rates of 84% have been reported (102).

4.1.4. Anxiety Disorders

Cross-sectional community (103, 104) and clinical studies (105–110) have found associations between anxiety disorders and suicide and attempted suicide in univariate models. However, there are questions regarding 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 (111). The association of panic disorder and suicidal behavior seems to be mediated by psychiatric comorbidity, particularly major depression (105, 107–110, 112). An analysis of pooled psychological autopsy results finds anxiety disorders (grouped with somatoform disorders) had an incidence of 2.5% in clinical populations, and 2.7% in general population suicides (71), however, that rate increases to 6.8% when anxiety disorders are one of multiple diagnoses. Some report that severe agitation or anxiety are associated with increased risk of suicide in mood disorders (113), and others find that anxiety is protective against suicide attempts in mood disorders (114).

Posttraumatic stress disorder has been associated, in clinical and community studies, with suicide attempt independently of comorbid major depression or substance use (115–119). The National Comorbidity Study found that PTSD was the only anxiety disorder independently associated with suicide attempts and ideation (120).

4.1.5. Alcohol and Substance Use Disorders

Substance use disorders, particularly alcohol, carry increased risk for suicidal behavior. Meta-analyses of psychological

autopsy studies report alcohol and substance use disorders in 17.6 to 25% of cases (71, 72). Murphy and Wetzel estimate the lifetime risk of suicide with alcohol dependence in outpatient and inpatient populations at 2.2% and 4.4%, respectively (121). Based on a meta-analysis, SMRs for suicide in alcohol and substance use disorders are 5.9 and 14 to 20, respectively, and higher rates for polydrug use (15–44) (75). Alcohol and substance use are frequently comorbid with other high-risk disorders, particularly mood disorders, and personality disorders (122). In psychological autopsy studies, comorbid alcohol and substance use disorders and Axis I disorders were present in 23 to 47% of suicides (68, 71). Acute alcohol intoxication is also a risk factor, and autopsy studies have detected the presence of alcohol in 20 to 50% of people who die by suicide (123).

4.1.6. Neuropsychiatric Disorders

In their meta-analysis, Harris and Barraclough report increased risk of death by suicide in Huntington's disease (3-fold increase), epilepsy (5-fold 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 (75). That analysis 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, was diagnosed in 4% of subjects (124, 125). Meta-analysis found 6.3% of suicides with medical/substance-induced mental disorders—with 15% in inpatients and 2.1% in the general population (71).

4.1.7. Comorbidity

Comorbidity is frequent in psychiatric disorders, and certain comorbidities have been found increase risk of suicide and suicide attempt. Psychological autopsy studies have found that 70 to 80% of suicides had more than one psychiatric diagnosis (126–132). Comorbid mood disorder and substance use disorders were reported in 19 to 57% of suicides in psychological autopsy studies (68, 71). Substance use disorders also increases the risk of suicide attempt in schizophrenia (127). Suicide attempts are also more frequent in mood disorders patients with comorbid personality disorders, particularly Cluster B personality disorders (128, 129), alcohol and substance use disorders (130, 131), or comorbid PTSD (132).

4.2. Special Populations

4.2.1. Adolescents

Suicide is the third leading cause of death among young people, defined as aged 15 to 25 years, in the United States (133). In 2003, 3,968 young people died by suicide, with young men having a suicide rate of 16/100,000 and young women, 2.7/100,000 (133). This represents a decline since 1990, from 22/100,000 in young men and 3.7/100,000 in young women.

Psychological autopsy studies of smaller samples of 21 to 53 adolescent suicides report diagnoses of depressive disorder in 51 to 85% of cases, substance use in 30 to 62%, conduct disorder in 22%, attention deficit disorder in 26%, and personality disorder in 31% (134–136). In many cases, these disorders were comorbid, and Shafi et al. (1988) found that 81% of adolescent suicides had more than one diagnosis (134). 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% had a disruptive disorder (137). 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 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, whereas a larger number of students made less serious attempts (138). Meta-analysis of population studies comprising 500,000 adolescents found that 9.7% (2–30%) reported a suicide attempt, with the rate in female adolescents twice that of male adolescents (139). Female individuals, both in the pediatric age range and in early adulthood, make more suicide attempts compared with male individuals. The ratio is reversed for completed suicide.

4.2.2. Older Adults

Disproportionally high suicide rates are also found among the elderly. Those older than 65 years comprise 13% of the US population but account for 20% of all suicide deaths (140). Suicide rates increase with age in men and not women in the United States (see Table 33.1), and, thus, the male-to-female ratio for suicide increases, such that older men had a 7.5-fold higher rate of suicide than older women in 2003. In 2003, for men older than 65 years, the suicide rate was 41.6, and in men older than 85 years, it reached 47.8, whereas for women older than 65 years, the suicide rate 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 older than 65 years declined from 17.9 to 14.6% in 2003. A review of 10 psychological autopsy studies in adults 65 years and older, found major psychiatric illness in 71 to 97% of late-life suicides. Major depression was diagnosed in 46 to 87% of suicides, substance use disorders in 3 to 43%, but primary psychotic illness and personality and anxiety disorders were not frequently diagnosed, nor was dementia (141). Physical illness is more prevalent in older adults, and prospective studies have found that certain illnesses increase risk for suicide (142). An uncontrolled psychological autopsy found physical illness in 70% of suicides older than 60 years (143), 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 (141).

Attempted suicide is less frequent later in life, with a ratio of approximately 4 attempts for every suicide (9), compared with a ratio of 10 or 20 attempts to one suicide in teens or young adults. Older suicides display a greater determination to die, giving fewer warnings and engage in greater planning than in younger age groups (144–146). They also are more likely to live alone, reducing chances of detection and rescue.

4.3. Other Risk Factors

Although psychiatric disorder seems 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, hopelessness, a reported history of physical or sexual abuse during childhood, a history of head injury or neurological disorder, and cigarette smoking.

4.3.1. Aggression and Impulsivity

Aggression is higher in suicide attempters compared with non-attempters, and in suicides (147). Elevated aggression has been associated with serotonergic dysfunction (148, 149), and there is some indication that aggression may be heritable (57). 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 function and ventral prefrontal cortical function and structure, a neurotransmitter system and brain region that may underlie behavioral inhibition 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 (150), and more parent- and teacher-reported aggression in middle childhood (ages 8–10 years) (151). Suicide attempters are more impulsive than non-attempters (17), and disorders that are characterized by high levels of impulsivity, such as borderline personality disorder, have high rates of suicide attempts; however, impulsivity is inversely correlated with lethality of suicide attempt (27,152,153). Thus, when suicide attempters are more impulsive they tend to make less lethal attempts, perhaps because of lack of planning and not taking precautions to prevent discovery and rescue. 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 (70).

4.3.2. Hopelessness

Beck et al. (1974) define hopelessness as "a system of cognitive schemas whose common denominator is negative expectations about the future" (154; p.864). In prospective and retrospective studies, hopelessness is associated with more severe suicidal ideation (155–157), suicide attempts (155, 157–161), and suicide (155, 157, 162, 163). Correlation between hopelessness and suicidal behavior has been documented in different age groups, including children/adolescents (164–166) and the elderly (167), and across different psychiatric disorders, including mood disorders (158, 160), schizophrenia (161, 168), personality disorders (169), substance abuse (170), and in community samples (155, 171). It is thought that a tendency to experience 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 (16).

4.3.3. Childhood Abuse

Childhood abuse, both physical and sexual, has been associated with suicide attempts in depressed patients (172), and in the community, where the relationship was largely mediated by psychiatric illness, but a part of the variance remained above and beyond psychiatric disorder (173). Childhood abuse increases the likelihood of developing psychiatric illness (174), the main risk factor for suicidal behavior. Preclinical studies have shown that early life adversity has lasting neurobiological consequences, including in abnormalities in the serotonergic system (175) and HPA axis stress response (176), both of which have been associated with suicide (21). Moreover, childhood abuse seems to increase the likelihood of developing impulsive/aggressive traits, which also increase risk for suicidal behavior (177).

4.3.4. Head Injury

Traumatic brain injury is associated with high rates of psychiatric illness (178, 179), suicidal ideation (178, 180), suicide attempts (179, 181), and suicide (182). Suicidal behavior among those with brain injury is often in the context of depressive disorders, anxiety disorders, and substance abuse or dependence (178), 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 (179). This may be caused, in part, by increased aggression, because more aggressive individuals tend to have more brain injuries (181), and greater aggression increases the risk for suicidal behavior.

4.3.5. Smoking

Cigarette smoking has been associated with suicidal behavior across diagnostic categories (16), and cigarette smoking predicts suicidal behavior in follow-up studies in mood disorder patients (17). The relationship between smoking and suicidal behavior, in part, may be related to neurobiologic dysfunction, because decreased serotonergic function was found among smokers in a diagnostically varied group (183).

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 with surviving suicide attempters (184–189). In case–control psychological autopsy studies, prevalence of "adversity" in the 3 months before suicide was reported in 29 to 93% of suicides compared with 5 to 88% of control subjects (68). In both alcohol and psychoactive substance use disorders, loss of close interpersonal relationships were noted within the 6-week period preceding suicide (190, 191). For adolescents and children, psychosocial factors including parent–child conflict, adverse life events, personal relationships, and family history of depression and substance abuse, seem to play an important role, comparable to that of psychiatric illness (47). 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 there are more female suicides in China than male suicides (70).

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 men and women, at greater risk for suicide mortality than the employed (192). 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 (193), particularly for older adults (93, 194).

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 2003, in the United States, 55% of male and 33% of female suicides used firearms (2). Among men 65 years and older, 79.7% of all suicides used firearms (2). In a psychological autopsy of adolescent suicides, the presence of a firearm in the house was a significant risk factor for suicide (195). A recent study of household firearm ownership rates and suicide rates in the United States from 1981 to 2002 study 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 the 0 to 19 years age group (196). In other countries, such as Sri Lanka and China, the ready availability to toxic agricultural chemicals also means that more impulsive suicide attempts are more often fatal (197).

4.4. Protective Factors—Reasons for Living

Although the preponderance of suicide research focused on identifying risk factors, there is an emerging interest in protective factors. The Reasons for Living Index was developed to assess the beliefs and values held by individuals toward suicide, and higher scores on that scale distinguish suicide attempters from non-attempters (198, 199). Religious beliefs, moral objections to suicide, survival and coping beliefs, and family responsibilities also seem to have protective effects against suicidal behavior (200–203).

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 to reduce the diathesis or propensity to attempt suicide (see Hirschfeld (204) for a review).

5.1. Recognizing and Treating Psychiatric Disorders

Failure to diagnose psychiatric illness leaves patients untreated and vulnerable to suicide (205). A diagnosis of MDD, of alcohol/substance abuse, or of schizophrenia already places the patient at a many-fold 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.

Most suicides have had contact with a primary care physician within a month of death (206, 207), and this high level of medical contact increases the opportunity for effective treatment intervention. Depression and other psychiatric disorders are underrecognized and undertreated in the primary care setting (208, 209) and fewer than one in six patients who die by suicide in the course of a major depressive episode were receiving adequate antidepressant treatment (210). 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 declines in suicide rates (211–214), 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 (215) and clozapine in schizophrenia (216, 217). Although ecological studies of suicide rates and antidepressant prescriptions rates show declines in suicide rates in adults and youth in Hungary (211), Sweden (218), Australia (219), and the United States (220, 221), meta-analyses of clinical trials of antidepressants have generally not detected benefit for suicide or suicide attempts in mood and other psychiatric disorders (222–224). This may be caused by 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. Further studies are required in high-risk populations to ascertain whether there are specific anti-suicidal properties in antidepressants.

Presently, there is much debate regarding the risk of increasing suicidality with the use of the class of antidepressant drugs known as 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 Food and Drug Administration (FDA) pediatric antidepressant trials found that there were small increases in the risk of adverse event reports of suicidal thinking or suicide attempts in youths taking SSRIs and other new generation antidepressant drugs (225). However, systematic questionnaire data do not identify an increase in risk for suicidal ideation on SSRIs, raising questions regarding ascertainment artifacts in the adverse event report method (see Mann et al., 2006 (226) 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 (227, 228). Rather they indicate a possible beneficial effect and, moreover, that a negligible number of youth suicides are taking antidepressants at the time of death (229). 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, because suicide is the third leading cause of death in youth, and more than 90% of suicides in depressed youth are untreated at the time of death (229).

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 use. Table 33.2 shows domains of risk factors that can be evaluated to come to an assessment of the risk.

TABLE 33.2. 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	

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 previous 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, white, male living alone.

5.2.2. Current Risk Factors

Suicidal ideation that includes a plan for suicide or evidence of active preparation for a suicide attempt is a more serious portent of short-term risk. Detecting suicidal ideation may necessitate active inquiry on part of clinicians, particularly among male patients who are half as likely as female patients to report suicidal ideation to their doctor before suicide (230). 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.

Comprehensive assessment of psychiatric disorder, particularly major depression, including anxiety, insomnia, agitation symptoms, and feelings of hopelessness is crucial. Treatment history of depression is also important to consider, because suicide risk is increased in the period immediately after discharge from hospitalization (231). Current alcohol and substance use should also be assessed, as well as inquiring into current life events and stressors.

5.3. Management

Although some published guidelines on the management of suicidal patients are available (232), determining the type and level of intervention depends largely on clinical judgment. Over treatment is preferable to under treatment, given the serious consequences of a missed suicide attempt, although unwarranted hospitalization is burdensome on both the patient and resources.

For patients deemed to be at imminent risk, such as those expressing severe suicidal ideation, a definite plan, and ready access to lethal means, hospitalization should be considered. For individuals at high, but not imminent risk, increased vigilance is necessary, including more frequent visits and/or telephone contact, and, if possible, enlisting the assistance of a family member or other close individual. 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 electroconvulsive therapy (ECT) for patients with treatment-resistant or psychotic depressions, and treatment for alcohol/substance, if present.

Because traits contribute to the diathesis that determines suicidality risk, longer-term treatments need to be considered, such as psychotherapies to improve problem solving, reduce hopelessness, and to 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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Clinical Psychopharmacology and Other Somatic Therapies

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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 Anxiety disorders · Bipolar disorder · Dementias · Major depression · Psychopharmacology · Schizophrenia · Sleep medications

1. Schizophrenia and Other Psychoses

The chemical antipsychotic classes (e.g., phenothiazine, butyrophenone, thioxanthene, dihydroindolone, and dibenzoxazepine) introduced in the United States 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, and aripiprazole. 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 drugs are primarily used for the treatment of schizophrenia, schizoaffective disorder, and bipolar disorder, manic phase (1, 2).

1.1. Antipsychotics: Efficacy

1.1.1. Schizophrenia

As a treatment for patients diagnosed with schizophrenia, FGA improvement rates range from 40 to 75%. All FGA are equally efficacious (3). A meta-analysis of controlled trials reported that clozapine, olanzapine, and risperidone produced a significantly better response than FGA or the SGA, quetiapine, ziprasidone, and aripiprazole (2). A previous meta-analysis concluded there was no evidence that SGA were more effective than FGA (4). 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).

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, whereas SGA are associated with modest improvements (8). However, high doses of FGA leading to ADR and concomitant

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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). Recent literature reports that improvement occurs within several hours or days after initiation of the antipsychotic, although the greatest degree of improvement occurs within 4 to 6 weeks (10). It is recommended that patients receive an adequately dosed antipsychotic trial of at least 4 weeks before considering a change in treatment. Being the drug of "last resort," the trial period for clozapine is 3 months. Long-term studies indicate that the maximum therapeutic benefit with FGA and SGA excluding clozapine may take up to 3 to 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 to 90% during the next 2 to 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- to 2-year period without symptoms to determine whether there is a continuing need for medication (14).

1.2. Second-Generation Antipsychotics

1.2.1. Efficacy

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 with 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%) because of metabolic symptoms (glucose, lipid) or weight gain. Perphenazine was discontinued in 22% of patients because of extrapyramidal side effects (EPS) (16).

Clozapine's efficacy has been compared with multiple FGA. In 8 of the 12 studies, clozapine was more effective than the reference antipsychotic, 3 studies demonstrated equal efficacy, and 1 study found clozapine to be less effective. Clozapine, because of 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 that they are effective. More studies for longer durations need to be conducted.

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), an FGA, or an SGA plus an 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 used (1, 15). However, because many studies have not used 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 US 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 approved for the reduction of risk of recurrent suicidality in patients with schizophrenia or schizoaffective disorder (19).

Of drugs available in the United States, 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 in which 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 approximately 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 $9,000 to $14,000 in "mental health services" after 2 years of treatment (22). Clozapine studies indicate that negative symptoms respond as well as positive symptoms (23).

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. The second study reported no benefit for the combination (24, 25). 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 the coadministration.

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 used 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 nonblinded reports (26).

1.2.4. Mania

All SGA, with the exception of clozapine, are approved by the FDA for the treatment of acute mania (27). Clozapine has been reported effective for mania in uncontrolled studies and retrospective reports (26). Controlled trials have reported onset of action of 2 to 7 days for risperidone, olanzapine, ziprasidone, and aripiprazole; and 21 days for quetiapine (28). Most studies that have compared lithium with SGA for treating patients diagnosed with acute mania have not used therapeutic lithium levels, and treatment response for most of those studies was considered greater than 50% symptom reduction, not complete resolution. Major treatment guidelines for bipolar disorder conclude that primary mood stabilizers are first-line treatment for acute mania (29). If an SGA is combined with a primary mood stabilizer, it should be discontinued once complete resolution of symptoms has occurred.

Olanzapine and aripiprazole are the two SGA approved for maintenance or prophylactic, treatment of bipolar illness. However, their efficacy, as compared with proven treatments such as lithium, is not well established, because most data compare these agents only to placebo (27, 29). Therefore, primary mood stabilizers are recommended for maintenance treatment.

1.2.5. Cognitive Disorders

Psychotic symptoms among patients with cognitive disorders can lead to behavioral disturbances, during which, patients may become hostile, agitated, aggressive, and dangerous to themselves and others or to their surroundings (30). The efficacy of SGA have been investigated in seven controlled trials, including two trials with risperidone, four trials with olanzapine, and one trial with quetiapine for the treatment of psychosis and behavioral disturbance in Alzheimer's disease (31). The studies generally reported that 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. More controlled studies are needed to determine the efficacy of SGA and FGA in the management of behavioral disturbances and psychosis in dementia.

1.2.6. Dosing: Second-Generation Antipsychotics

Current recommendations for changing from one antipsychotic to another include a cross-taper, in which current medication would be tapered for 4 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.

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 2-week increments (33).

1.2.6.2. 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 to 50 mg/day, if tolerated. The usual target dose range is 300 to 450 mg/day, administered either twice daily or three times daily. 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 24 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).

1.2.6.3. 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 1 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. Because of 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 to 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 2 weeks have been successfully maintained on olanzapine monotherapy at a dose of 5 to 20 mg/day. 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 intramuscular 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.

1.2.6.4. Risperidone

The recommended titration schedule for risperidone used in the treatment of schizophrenia is 1 mg twice daily for 1 day, 2 mg twice daily for 1 day, and 3 mg twice daily thereafter. Further dose changes should be no faster than increments of 1 mg/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 to 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 intramuscularly every 2 weeks. Clinical effects from dosage adjustments (including initial dosing) should not be expected earlier than 3 weeks after 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 2 weeks. Doses should be given every 2 weeks. Before 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 intramuscular injection should be administered with the safety needle provided in the drug packaging for the health care professional's use. The drug is administered by deep intramuscular gluteal injection. Injections should be alternated between the two buttocks (38). 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).

1.2.6.5. 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 two or three doses, may be reached by the fourth day. The average dose in clinical trials ranged from 300 and 400 mg daily as two or three divided doses, although efficacy has been demonstrated in the dose range of 150 to 750 mg daily. 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 longer than 1 week, the medication must be re-titrated; however, if the patient has missed less than 1 week, titration of dose is not required (40).

1.2.6.6. 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 greater than 200 mg daily has not been studied, and justification and electrocardiographic (ECG) monitoring is recommended to be documented on the patient's record if the patient's dose exceeds 160 mg/day. It is recommended that patients should be monitored for treatment response for several weeks before 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 regarding 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.

1.2.7. Adverse Effects

This section discusses ADR of the SGA. Specific information regarding certain agents is included within the summaries.

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 after 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.

1.2.7.2. Cardiovascular

Hypotension or dizziness are observed with clozapine during the initiation of treatment and/or after dose escalation, at an estimated incidence of up to 13%. Risperidone, olanzapine, and quetiapine have also been reported to cause dizziness and orthostasis (36, 39, 40); however, 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. At a dose of 10 mg/day, olanzapine produced an increase of 3.6 mmHg in standing systolic blood pressure as compared with 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 per minute (bpm). Quetiapine is 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 United States, the United Kingdom, 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 to 14 ms more than with risperidone, olanzapine, quetiapine, and haloperidol; but 14 ms less than with thioridazine. There has been no indication in postmarketing surveillance that the effect of ziprasidone 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 those seen with FGA (44). Risperidone was reported to lengthen QTc interval in phase III trials; however, a subsequent review found no evidence that risperidone was associated to 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).

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.

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

(50, 51). Clozapine and olanzapine, risperidone, and quetiapine are the SGA most commonly indirectly associated with diabetes (51). This is not surprising because these antihistaminic drugs are more likely to cause significant weight gain than ziprasidone and aripiprazole, thereby, increasing the risk of diabetes. However, the FDA decided in 2004 that, because of a lack of data regarding 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 greater than 6 mg/day (54). Olanzapine at doses between 20 and 40 mg/day have 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). Amenorrhea, galactorrhea, and gynecomastia have not been reported with clozapine. Amenorrhea and galactorrhea are reported in 10% of female patients receiving risperidone. 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 in trials lasting 6 to 8 weeks. Olanzapine was greatest, at 29%, followed in descending order by quetiapine (23%), risperidone (18%), ziprasidone (10%), and aripiprazole (8%). The magnitude of the weight gain with olanzapine and other medications is probably dose dependent (58).

Lipid Abnormalities. Clozapine and olanzapine are four to five times more likely to be associated with elevations in triglyceride levels, but risperidone is not (51). Quetiapine was associated with 11% increases in cholesterol and 17% increases in triglycerides (40). Lipid abnormalities have not been reported with ziprasidone or aripiprazole (33,41).

1.2.7.4. Hematologic

Clozapine has been reserved for patients with treatment refractory schizophrenia because of 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 United States 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 3 months of treatment. Risk factors include the first 3 months of treatment, older age, female sex, and a 15% or greater spike in white blood cell counts (WBC) (59, 60). At this time, a baseline and weekly WBC with differential is required for the first 6 months of treatment. During the subsequent 6 months, WBC must be monitored every other week. After that time, WBC must be monitored every 4 weeks for the duration of treatment. Current guidelines indicate that clozapine should be immediately discontinued if the total WBC falls to less than 3,000 cells/mm^3 or the absolute number of polymorphonuclear leukocytes falls to less than 1,000 cells/mm^3. The patient should not receive clozapine again, because 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.

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 aminotransferase (AST) and ALT and gamma-glutamyl transferase levels were observed in 10% of patients and these elevations seem 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 quetiapine (40); transaminase elevations of greater than three times normal limits were reported in 6% of patients treated with quetiapine. These elevations occurred within the first 3 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).

1.2.7.6. Neuroleptic Malignant Syndrome

Cases of neuroleptic malignant syndrome (NMS) 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.

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).

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 anticholinergic potency (62).

Extrapyramidal Side Effects, Early Onset. Overall, the SGA are associated with a decreased risk for acute EPS as compared with 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. Because akathisia associated with FGA has been reported to improve with clozapine treatment, additional controlled studies need to be performed to assess this side effect in clozapine-treated patients. Risperidone at 6 mg/day produces fewer EPS than 10 to 20 mg/day haloperidol (64). Incidence and severity of EPS increase as the risperidone dose increases to greater than 6 mg/day. Although EPS have not been commonly reported in patients with schizophrenia, the manufacturer reports rates of 15 to 32% of patients, most commonly 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 equal to placebo for aripiprazole, although akathisia occurred slightly more frequently (33).

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 because risperidone causes less early onset EPS than FGA, the rate of tardive dyskinesia may be lower as well (66). Olanzapine and haloperidol comparisons across three studies showed a lower incidence of tardive dyskinesia with olanzapine (67). There are little data to report on quetiapine, ziprasidone, and aripiprazole, because 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.

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 and 900 mg daily (5). Between 22 and 74% of clozapine-treated patients may have abnormal electroencephalograms (EEG). Seizures have been reported in fewer than 1.0% of patients receiving risperidone, olanzapine, quetiapine, ziprasidone, and aripiprazole (39–41, 68).

1.2.7.9. Ophthalmologic

Quetiapine has been associated to cataract formation in dogs, therefore, the manufacturer has recommended monitoring by slit-lamp examination.

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 discontinuation, or "rebound psychosis" has been described, although some reports question this effect. 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 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-treated and 12% of quetiapine-treated patients (36, 40).

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 because of underreporting (39). Cases of enuresis associated with risperidone and olanzapine have also occurred; the manufacturer reports a 2% incidence of enuresis with olanzapine (36).

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.

1.2.7.13. Temperature Regulation

Hypothermia occurs with 87% of patients on clozapine (69). This effect, considered benign, is thought to be a central nervous system (CNS) effect.

Hyperthermia. A benign temperature elevation of 1 to 2°F has been noted within the first 5 to 20 days of treatment with clozapine. It is estimated to occur in 7 to 14% of patients. The temperature increase might indicate a possible infection secondary to leukopenia or, possibly, NMS. Patients with hyperthermia should have a complete blood count (CBC) and sedimentation rate performed to exclude 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 (39).

1.3. First-Generation Antipsychotics

The primary FDA-approved indications for FGA are schizophrenia, mania, and Tourette's syndrome.

1.3.1. Efficacy

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 2- to 3-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.

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 with first- and second-year relapse rates 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 a 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).

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 nonsignificant increases 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 plus one SGA, and two SGA or more (76). There is limited evidence to suggest that using two or more 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.

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.

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 regarding tardive dyskinesia (83).

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).

1.3.5. Dementia

The use of antipsychotic medications is regulated in long-term care facilities, rising from concerns regarding 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 patients to present a danger to themselves 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.

1.3.6. Dosage

All FGA are equally effective in treating psychotic disorders when given in equipotent doses (10). For example, 100 mg chlorpromazine is approximately equal in therapeutic use to 4 mg trifluoperazine, 100 mg thioridazine, 2 mg fluphenazine, 3 mg thiothixene, or 2 mg haloperidol (71). FGA can be divided into low (e.g., chlorpromazine) or high-potency (e.g., 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 regarding ADR. When switching a patient from one antipsychotic to another, Table 34.1 has been constructed to estimate the inter-drug milligram potencies of the typical antipsychotic drugs. The average dose of chlorpromazine was 734 ± 63 mg. 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 schizophrenic patients if not using either haloperidol or clozapine blood levels to dose the patient.

1.3.6.1. Schizophrenia, Nonagitated Patient

An oral dose of 300 mg/day chlorpromazine or its equivalent is considered a minimal therapeutic dose for the treatment of acute psychosis. Peak response occurred at approximately 600 mg/day chlorpromazine or its equivalent in dose–response studies of schizophrenic patients (87). Doses of chlorpromazine greater than 1,200 mg/day or its equivalent do not produce substantially greater improvement than smaller doses (71, 87). In addition, haloperidol dosed between 3 and 7.5 mg daily were found to be equally efficacious as, and 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 100 mg

TABLE 34.1. Potency classification and approximate equivalent doses of high- and low-potency FGA and SGA. Oral doses equivalent to 100 mg chlorpromazine.

Low-potency FGA	High-potency FGA	SGA
Chlorpromazine (100 mg)	Fluphenazine (2 mg)	Risperidone (2 mg)
Mesoridazine (50 mg)	Haloperidol (2 mg)	Olanzapine (5 mg)
Thioridazine (100 mg)	Loxapine (10 mg)	Aripiprazole (7.5 mg)
	Molindone (10 mg)	Ziprasidone (60 mg)
	Perphenazine (8 mg)	Quetiapine (75 mg)
	Thiothixene (5 mg)	Clozapine (50 mg)[a]
	Trifluoperazine (4 mg)	

[a] Dose changes made by the editor.

chlorpromazine or its equivalent administered two or three times daily. Gradual dose titration may occur at a rate of 100 to 200 mg/day chlorpromazine 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 with doses lower than 800 mg/day (87).

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 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 100 mg chlorpromazine orally or 25 mg chlorpromazine intramuscularly (or its equivalent) every 1 to 2 hours until agitation and 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, because it has an improved cardiovascular ADR profile (hypotension) over chlorpromazine. Dose administration of 2 to 10 mg haloperidol orally or intramuscularly (with dose correction) every 30 minutes to 2 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 during the preceding 24 hours, corrected for bioavailability differences (90). The intramuscular to oral ratio for chlorpromazine is 1:4 (e.g., 25 mg intramuscularly equals 100 mg orally) and haloperidol is approximately 1:2 (e.g., 2.5 mg intramuscularly equals 5 mg orally).

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).

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., EPS) (10).

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 to 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 that the majority of patients can be maintained on 300 to 600 mg/day chlorpromazine (or equivalent) (87).

1.3.6.6. Long-Acting Parenteral Antipsychotics

A review of five studies that lasted longer 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 15 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 regarding 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). Because of 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 10 to 30 mg fluphenazine decanoate every 2 weeks provides the greatest protection against relapse. Interestingly, 45 mg every 2 weeks 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 more recent study, 30% of the patients were managed with monthly injections during an 8-month period (100). Patients stabilized on fluphenazine decanoate should be considered for an increased interval between injections as a dose-reduction strategy. The greatest protection against relapse is provided with 10 to 30 mg fluphenazine decanoate every 2 weeks (87).

Oral haloperidol 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 to 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 nonloading-dose approach involves administering a calculated maintenance dose while the oral dose is tapered. A review of US studies indicated that a maintenance dose of decanoate (milligrams per month) to oral (milligrams per day) dose ratio of 10 to 15 was more reasonable than the European literature's ratio of 20 (101). For example, using the US 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 during 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., people older than 65 years of age) and in patients on 10 mg/day or less of oral haloperidol, the recommended loading dose is 10 to 15 times the oral dose (3). If a patient is receiving 10 mg/day oral haloperidol, the total loading dose is 20 times the 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 to 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 to 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 or 100 mg/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 10 mg/day fluphenazine might be added (95). The fluphenazine decanoate dose could

then be increased by 2.5 to 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 to 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.

1.3.7. Cognitive Disorders

1.3.7.1. Dementia

Dementia patients may be unusually sensitive to FGA therapeutic and ADR; therefore, low doses of 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.

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 with more EPS with high-potency FGA (i.e., haloperidol, perphenazine, fluphenazine, thiothixene) (110, 111).

1.3.8.1. Autonomic

The autonomic nervous system effects are caused by 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 mouth, 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 after abrupt discontinuation of FGA. Symptoms such as insomnia, headache, hypersalivation, diarrhea, nausea, and vomiting have occurred. Symptoms may begin 2 to 3 days after discontinuation, and may occur for up to 2 weeks. The incidence of withdrawal symptoms is 10 to 75%. Patients prescribed FGA for at least 1 month should undergo a taper of antipsychotic after discontinuation.

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.

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 monitoring ECG and serum potassium levels is recommended for patients at baseline and periodically during treatment. Patients with QTc greater than 450 ms should not be initiated with thioridazine, and if QTc is greater than 500 ms, patients should be discontinued. The FDA also recommends that patients taking pimozide should undergo baseline ECG and periodic follow-up (116–118).

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 to 10% of patients taking chlorpromazine within 14 to 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).

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 to 95% of women receiving FGA compared with 3 to 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, although 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.

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.

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%.

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, because of the potential to exacerbate psychosis (113, 125).

1.3.8.8. Neuroleptic Malignant Syndrome

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 2 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.

1.3.9. Neurologic

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).

1.3.9.2. Extrapyramidal Side Effects

EPS 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 younger than 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 50 mg diphenhydramine or 2 mg benztropine 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 to 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 to 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 middle-aged patients, with women twice as likely as men 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. On 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 may be beneficial, because 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 on 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. Similar to 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 EPS (i.e., low-potency drug), addition of conventional anticholinergics, such as benztropine, or addition of amantadine.

TABLE 34.2. Pharmacotherapy for extrapyramidal side effects.

EPS	Drug and Dose
Dystonia	50 mg diphenhydramine or 2 mg benztropine intravenously or intramuscularly immediately; may repeat intravenous dose in 5 min and intramuscular dose in 20–40 minutes
Akathisia	2–6 mg benztropine orally daily at bedtime 10–40 mg propranolol orally twice daily 5–10 mg diazepam orally three or four times daily 100–200 mg amantadine orally[a] either once or twice daily 0.1–0.4 mg clonidine orally twice daily
Parkinsonism	1–4 mg benztropine orally one to four times daily[a] 2–5 mg trihexyphenidyl orally two to four times daily[a]

[a] Dose changes made by the editor.

The condition disappears on discontinuation of drug therapy, but this may take several weeks to months, depending on the dosage and individual patient.

Tardive dyskinesia is a complex syndrome of hyperkinetic involuntary movements (112, 113). All antipsychotics have been associated with tardive dyskinesia, but real differences in incidences among antipsychotics, if they exist, are not obvious. These syndromes wax and wane over time, disappear during sleep, and they 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 biting 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, wavelike 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 to 40% of patients with tardive dyskinesia (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 to 20%. The incidence is estimated at 2 to 5% per year during 5 to 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, sex, psychiatric diagnosis, antipsychotic dose, and duration of antipsychotic exposure. Tardive dyskinesia usually has an insidious onset while the patients are still receiving antipsychotics, although abnormal movements often appear for the first time or increase dramatically after 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, tardive dyskinesia movements are not generally progressive and may improve or resolve (135, 137). Many agents have been used in attempting to treat tardive dyskinesia, 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 Movement Inventory Scale) performed at least yearly for tardive dyskinesia (137–139).

1.3.9.3. Sedation

Sedation 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).

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 less than 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)

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 to 3 kg. Vision usually is not impaired. Cornea and lens changes seem 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 seems to be a function of time and dose, rather than dose accumulation. Thioridazine in doses of at most 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.

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).

1.3.9.7. Sexual Disturbances

In men, sexual 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, therefore, 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 seem 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 to 80% of patients will become impotent. Management includes substitution of an antipsychotic of a different chemical class and close monitoring.

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).

1.3.9.9. Urinary

Enuresis or urinary incontinence has been associated with antipsychotics, and onset is often within 2 weeks of initiating treatment. Urinary retention may also occur, especially with medications having higher anticholinergic effects.

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.

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 (MDD); however, SSRI have been shown efficacious for a myriad of other disorders. Fluoxetine is FDA-approved for the treatment of MDD, bulimia nervosa, obsessive–compulsive disorder (OCD), panic disorder, and premenstrual dysphoric disorder, and has also shown efficacy for the following off-label disorders: MDD associated with alcoholism, MDD associated with diabetes, seasonal affective disorder, posttraumatic stress disorder (PTSD), obesity, hot flashes, migraine, headache prophylaxis, and fibromyalgia. Paroxetine is FDA-approved for the treatment of MDD, generalized anxiety disorder (GAD), OCD, panic disorder, PTSD, and social phobia. Sertraline is FDA-approved for the treatment of MDD, OCD, panic disorder, PTSD, premenstrual dysphoric disorder, and social anxiety disorder. Fluvoxamine is FDA approved for the treatment of OCD. Citalopram is FDA approved for the treatment of MDD. Escitalopram is indicated by the FDA for the treatment of MDD and GAD.

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, whereas 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. TCA were shown to be more effective in depressed inpatients. SSRI were better tolerated and discontinuation rates caused by ADRs were less with SSRI than TCA. 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 a 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, whereas patients with shorter duration of episodes (1–6 months) did not (145–148). Older patients are thought to show a preferential response to TCA versus SSRI (149), especially older women (150). It is suggested that men respond better to TCA treatment, whereas women respond better to SSRI treatment (151).

2.1.1.1. Major Depression with Melancholic Features

SSRI are less effective than TCA in treating the melancholic subtype of MDD (65). Studies that used strict remission criteria showed TCA response rates of 57 to 63%, as compared with 8 to 30% for fluoxetine and 15% for placebo.

It has been suggested that venlafaxine may also be more effective than SSRI for melancholic depression (152, 153). These studies suggest TCA are superior to SSRI in the treatment of melancholic depression.

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).

2.1.1.3. Major Depression with Atypical Features

In studies of agents in the treatment of "atypical depression," 20 to 60 mg/day fluoxetine and 50 to 300 mg/day imipramine were more effective than placebo. These findings differ from earlier data in which TCA were suggested to be inferior to MAOI (157–160).

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 greater than 0.8 mEq/L (161). More recently, 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 approved for the treatment of bipolar depression.

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, previous treatment failure, the presence of delusions, and age 35 years 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 4 should continue to week 6 of treatment, because many patients may become responders. However, if the patient has had no response by week 4, 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 SSRI 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 threefold to fourfold (166). Among patients who failed a 12-week citalopram treatment 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).

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 from 43 to 57% for placebo (169, 170)

2.1.1.7. Mood Disorder Caused by Medical Conditions

Symptoms of depression presenting in the medically ill may represent: 1) a major depressive episode that is independent of the medical condition; 2) an adjustment disorder with depressed mood precipitated by the stress of the medical illness; 3) secondary depression caused by a preexisting medical condition thought to have an 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 caused by medical conditions and secondary depression.

2.2. Mood Disorders Caused by Medical Conditions

2.2.1. Dementia of the Alzheimer's Type

The frequency of depressive syndromes in patients diagnosed with dementia of the Alzheimer's type (DAT) ranges from 17 to 31% (171). Treatment guidelines and limited clinical studies indicate that patients should be considered for antidepressant therapy even if they do not meet criteria for a depressive syndrome (172, 173). The severity of dementia and the spectrum of depressive symptoms must be considered, because 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 at least 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 (ADL), 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.

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 (RCT) published in this population comparing any SSRI to other antidepressants or placebo. However, one 6-week RCT demonstrated that 75 mg/day amitriptyline and 75 mg/day nomifensine were more effective than placebo in the treatment of epileptic patients with major depression (176). 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, because antidepressants and anticonvulsants are both classes of medications with a high potential for interacting with metabolism.

2.2.3. Multiple Sclerosis

Major depressive episodes are estimated to range between 40 to 70% of patients with multiple sclerosis (MS) (177). In 79% of 43 interferon beta-1b-treated patients affected by MDD associated with MS, 200 mg/day fluvoxamine for 3 months was effective (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).

2.2.4. Stroke

Eighteen percent of patients recovering from stroke experienced a major depression within 2 months of the occurrence (180). The effectiveness of antidepressant therapy of medications, including nortriptyline at doses up to 100 mg/day, 20 mg/day fluoxetine, citalopram at doses up to 40 mg/day, and trazodone at doses up to 200 mg/day, in dysthymic and depressed poststroke patients has been documented (182–185). 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).

2.3. Secondary Depression with Medical Illness Disorders

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).

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 diabetic patients 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).

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). In women diagnosed with fibromyalgia with or without a concomitant diagnosis of major depression, 60 or 120 mg/day duloxetine was more effective than placebo in reducing pain scores (194). A meta-analysis of nine RCT involving TCA suggested that the greatest improvement from the antidepressants was associated with sleep quality, whereas only modest improvement was found in measures of stiffness and tenderness (192).

2.3.4. HIV Seropositivity

An estimated 4 to 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 whereas 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.

2.3.5. Myocardial Infarction

It is that estimated 45% of patients admitted for a myocardial infarction (MI) will develop symptoms of major or minor depression within 8 to 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 nine 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-MI patients as well as in coronary artery disease patients without MI. Therefore, clinicians are advised to treat major depression when present in this patient population (198). TCA are contraindicated in the first 6 weeks after an MI, because of their cardiovascular-related ADR profile (199). An RCT contrasting the effectiveness of fluoxetine to placebo among patients 3 months after MI who were also diagnosed with MDD failed to show a difference between the two treatments (200). A case–control study involving nearly 8,700 patients exposed to antidepressants after 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 antiplatelet effects of the drugs (201).

2.3.6. Postpartum Depression

Postpartum depression affects approximately 10 to 15% of childbearing women (202). Prophylactic nortriptyline at doses up to 75 mg/day was successful in preventing depression recurrence in postpartum patients with a previous history of postpartum illness (202). Untreated patients were found to experience a 63% recurrence rate whereas only a 7% rate was found in the treated patients. Fluoxetine was significantly more effective than placebo after 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).

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 patient 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).

2.5. Dosing

The dosage usually recommended for fluoxetine is 20 to 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 20 mg, 40 mg, and 60 mg fluoxetine with 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 to 6 weeks. The usual dose of paroxetine for depression is 20 to 50 mg daily. This medication can be taken at bedtime because it is considered the most likely of the SSRI to cause sedation. The initial starting dose is 20 mg daily for 2 to 3 weeks and can be titrated weekly in increments of 10 mg. A comparison study found equivalent efficacy with mean doses of 31 mg paroxetine daily and 42 mg fluoxetine daily (211). The usual recommended antidepressant dose for sertraline is 50 to 200 mg daily. Sertraline may be taken in either the morning or the evening in one dose. The initial dose is usually 50 mg daily for 2 to 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 (although not indicated for depression) is 50 to 300 mg daily. Doses greater than 150 mg daily should be split in two doses. Daytime doses may be taken with food to minimize gastrointestinal ADR. The usual recommended dose of citalopram is 20 to 40 mg daily. Initial dosing is usually 20 mg daily for 1 week. In a fixed dose trial, 10 to 20 mg escitalopram daily was found to be as effective as 40 mg citalopram daily (213). A summary of the usually recommended doses of the antidepressants is presented in Table 34.3.

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 SSRI.

2.6.1. Cardiovascular

The SSRI do not affect blood pressure, but may cause slight decreases in heart rate. There are no data to expect SSRI are cardiotoxic; and arrhythmias after overdose are very 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 people not using antidepressants (214).

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
Serotonin–norepinephrine reuptake inhibitors			
Duloxetine	Cymbalta	20	20–60[a]
Venlafaxine	Effexor	75	75–375
Serotonin–norepinephrine reuptake inhibitors (tricyclic)			
Amitriptyline	Elavil	50	50–300
Amoxapine	Asendin	100	100–600
Clomipramine	Anafranil	75	75–250
Desipramine	Norpramin	75	75–300
Doxepin	Sinequan	75	75–300
Imipramine	Tofranil	50	50–300
Nortriptyline	Pamelor	50[a]	50–150[a]
Protriptyline	Vivactil	10	10–60
Trimipramine	Surmontil	50	50–300
Serotonin–norepinephrine reuptake inhibitors (tetracyclic)			
Maprotiline	Ludiomil	75	75–300
Dopamine–norepinephrine reuptake inhibitor			
Bupropion	Wellbutrin	150[a]	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 h	6–12 mg/24 h
Tranylcypromine	Parnate	20 mg[a]	20–60 or 0.7 mg/day[a]

[a] Dose changes made by the editor.

2.6.2. *Central Nervous System*

Anxiety/agitation, tremor, and insomnia associated with SSRI are symptoms thought to be a hyperstimulation or akathisia-like reaction. This usually lasts approximately 1 month (215). Approximately 10 to 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, including tremor, myoclonus, hyperreflexia, ankle clonus, muscle rigidity, ataxia, and incoordination; gastrointestinal symptoms, such as nausea, vomiting, and diarrhea; and disseminated intravascular coagulation. Hyperthermia is associated with potential lethality. MAOI should be discontinued for at least 2 weeks before initiating therapy with another serotonergic antidepressant, and five half-lives of serotonergic drugs (and their active metabolites) should pass before 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 SSRI. In reports inquiring regarding patients' sexual function, the incidence of sexual dysfunction ranged from 34 to 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 antidepressant studies, which showed that the rates of suicide were similar between the SSRI, comparator antidepressants, and placebo (220). However, recently, 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% for placebo to 4% for SSRI and other second-generation antidepressants (221). The FDA report has been strongly challenged by a study of more than 24,000 adolescents diagnosed with MDD, which concluded that antidepressant use had no effect on the likelihood of suicide attempts (222).

When SSRI are to be discontinued, tapering should occur during 1 to 2 weeks to avoid withdrawal symptoms, with the exception of fluoxetine. Patients discontinuing paroxetine, fluvoxamine, sertraline, and fluoxetine experienced withdrawal reactions, at respective rates of 14, 20, 2.2, and 0% (223). Criteria for SSRI withdrawal include two or more of the following symptoms within 1 to 7 days after discontinuation of 1 month or more of SSRI treatment: dizziness, lightheaded, vertigo, paresthesias, anxiety, diarrhea, fatigue, gait instability, headache, insomnia, irritability, nausea, tremor, and visual disturbances (224).

Similar to the TCA, the SSRI can cause "switching" of patients symptoms from depression to hypomania/mania, most commonly in patients with bipolar illness.

2.6.3. *Gastrointestinal*

The nausea associated with SSRI is generally mild, transient, rarely associated with vomiting, and more prevalent with SSRI than TCA. 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 case 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). Fluvoxamine was found to cause weight loss in nonvomiting eating disorder patients (227).

2.6.4. Hematologic

Serotonin potentiates platelet activation. SSRI decrease serotonin uptake from blood to platelets. Because platelets do not synthesize serotonin, SSRI are associated with increases in bleeding episodes. Similar bleeding risk was not associated with nortriptyline, protriptyline, desipramine, trimipramine, maprotiline, and amoxapine.

2.6.5. Renal

All SSRI 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.

2.7. Third-Generation Antidepressants

2.7.1. Indications

Third-generation antidepressants (TGAD) consist of amoxapine, bupropion, duloxetine, maprotiline, mirtazapine, trazodone, venlafaxine, and nefazodone. All agents are FDA-approved for the treatment of MDD. Amoxapine is also approved for MDD with psychotic features, and venlafaxine is also approved for generalized anxiety disorder.

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 Sprier TCA.

A meta-analysis of SSRI compared with venlafaxine trials suggested that venlafaxine was associated with a 7% higher remission rate (229). This finding was not observed between venlafaxine and the TCA and mirtazapine. Duloxetine is an agent similar in mechanism of action to venlafaxine. The studies of duloxetine found the drug to be as effective as 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 10 (45%) of 22 treatment-refractory depressed patients in a 4-week trial (231). A 4-week trial of amoxapine was as effective as an amitriptyline plus perphenazine combination in treating MDD with psychotic features (232). The combination showed slightly better global ratings, but with a greater incidence of EPS. Similar to all other antidepressants, TGAD are effective in preventing relapses of depression. Bupropion was equal to amitriptyline in a 6- to 12-month follow-up study (233). Maprotiline, at 75 mg/day, administered prophylactically to 1,141 patients for 1 year resulted in a 16% relapse rate, in contrast to a 32 to 38% relapse rate for patients treated with placebo (234).

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 to 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 TCA, and also have been some reports of a premature loss of efficacy after 6 to 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 every morning and then increased to 150 mg twice daily on 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. The 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 before 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 to 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, sex, or smoking. There is no evidence that doses greater than 60 mg/day are more effective than 40 to 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, because 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 TCA are 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 a 30 mg dosage and then further increased to a 45 mg dosage, if needed, at intervals of 1 to 2 weeks (236). At doses greater than 45 mg/day, the sedating properties of the drug are blunted by increased norepinephrine agonist activity at the 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 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).

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 should be initiated at no shorter than 4-day intervals. In severely depressed or hospitalized patients, the recommended starting dose is 75 to 150 mg/day, which may then be increased further during the next 7 days. The minimum effective dose of venlafaxine is 75 mg/day, with a maximum dose of 375 mg/day administered in two or three 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 to 225 mg/day, which seems 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 during a 7- to 14-day period (236).

A summary of the usually recommended doses of the antidepressants is presented in Table 34.2.

2.7.4. Adverse Effects

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 incidences are similar to amitriptyline and imipramine, as are the incidences of orthostatic drops in blood pressure and sedation. Atrial flutter and fibrillation and conduction defects similar to those associated with the TCA 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. 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).

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 pruritus occur at doses of 300 to 900 mg/day. The maculopapular rashes clear in 3 to 4 days after drug discontinuation. Pruritus alone usually will clear with a reduction in dosage. A transient weight loss of at least 5 pounds has been found to occur during a 3- to 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 0.80% (37/4,259). The incidence is 0.44% (15/3,395) in patients receiving doses no greater than 450 mg/day, whereas the rate for doses greater than 450 mg/day demonstrated a fivefold increase of 2.2% (19/864). Seizure risk factors included a history of bulimia, doses greater than 450 mg/day, and a history of seizures. Because bupropion has dopamine agonist activity, it is questionable whether to use the drug in the treatment of delusion or hallucinating patients (65). Although the drug has been used in schizophrenic patients as a smoking cessation treatment (240), nicotine replacement is indicated before bupropion treatment.

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 1 week. Other adverse events reported include diarrhea and fatigue. Diastolic blood pressure in 9-week trials was reported to increase an average of 2 mmHg. 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)

2.7.4.4. Maprotiline

Because this antidepressant is a molecular manipulation of the TCA, it is not surprising that its ADR profile is similar to TCA, 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 nonpruritic. 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).

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 with 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, 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).

2.7.4.6. Trazodone

The most common ADR with trazodone is sedation. Anticholinergic ADR are not associated with trazodone. Initially trazodone was considered a noncardiotoxic 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 TCA in that it is transient; it only lasts for approximately 4 to 6 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 it has been reported in up to 45% of patients. There are reports of hepatoxicity within the first few weeks of trazodone therapy that is 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 rate of 1 in 6,000 male patients because of the voluntary reporting nature of the system (65).

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 with 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).

2.8. Tricyclic Antidepressants

2.8.1. Efficacy

Patients with MDD 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 TCA 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 used is dependent on 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.

2.8.2. Indications

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 with 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 TCA, however, the management of these treatment-resistant patients is an appropriate question. Electroconvulsive therapy (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 control subjects (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 to 1,200 mg/day producing concentrations in excess of 0.3 mEq/L are sufficient.

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 TCA will respond to ECT (246). Although 66% of nondelusional, depressed patients respond to TCA, only 34% of delusional depressed patients respond to a 3-week trial of TCA. 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 to 150 ng/ml would be a reasonable initial target concentration. If the patient does not respond, higher doses

may be used. Antipsychotic drugs interact with TCA to increase their concentrations. Thus, it is hypothesized that the ineffectiveness of TCA in treating delusional depression may be the result of using subtherapeutic doses. Only 41% of delusional depressive patients 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 antipsychotic. 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 depressive patients resulted in response rates of only 32% after 3 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 9 weeks.

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 2 years, with the greatest risk of relapse occurring within 4 to 6 months of the initial remission. Finally, 15 to 20% of patients with recurrent depression do not fully recover from any given episode (249). 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).

2.8.3. Dosing

2.8.3.1. Empirical Dosing

When empirically dosing patients with TCA 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 to 50 mg every 1 to 2 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.

2.8.3.2. Therapeutic Trial

Commonly, 4 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 4, the medication should be changed; however, if a partial response or improvement has been noted, the patient should continue the trial until week 6 (254). Of nondelusional depressed patients who respond to TCA, it has been reported that 88% do so within 3 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 to 6 months after the initial remission (249). At the end of this period, the outpatient should be tapered off of the TCA 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) because 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).

2.8.3.3. Blood Levels

A review of the studies examining the relationship between the antidepressant effect of TCA 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 ($\geq$116 ng/ml) was 51%, compared with only 15% below the threshold. For nortriptyline, the therapeutic window of 58 to 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 TCA, there is not enough data available in the literature to come to any firm conclusion regarding the validity of plasma concentrations measurements. Because absorption and tissue distribution of a TCA may take as long as 5 to 8 hours, it is recommended that steady-state plasma sampling be carried out at approximately 12 hours after the last dose. A 12-hour sampling times guarantees that plasma levels are being measured during the elimination phase of the tricyclic, which, in contrast with 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 1 week).

2.8.3.4. Retrospective Dosing

Because TCA 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 used as a reasonable approximation of the 12-hour steady-state level (256).

2.8.4. Adverse Effects

From a practical standpoint, the TCA are classified as either dimethylated, or tertiary amine, TCA, (amitriptyline, imipramine, doxepin, and trimipramine) or monomethylated, secondary amine, TCA (nortriptyline, desipramine, and protriptyline). The dimethylated amine TCA primarily block serotonin reuptake, whereas the monomethylated amine TCA primarily block norepinephrine reuptake. Dimethylated TCA are clinically considered to be more sedating, more potent as anticholinergic agents, and cause greater weight gain than the monomethylated TCA. Monomethylated TCA cause less postural hypotension than the dimethylated class (257).

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 approximately 1 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. TCA can increase intraocular pressure in patients with closed-angle but not open-angle glaucoma. An in vitro estimation of the anticholinergic potency of the TCA 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).

2.8.4.2. Cardiovascular

The most common cardiovascular problem precipitated by TCA use is orthostatic hypotension. The problem can be minimized by using nortriptyline. Among patients with first-degree atrioventricular (AV) block, there has been found to be a small risk of progressive block. If TCA are used, ECG and TCA concentration monitoring is necessary. Patients with bundle-branch blocks have 10 times increased risk of developing a 2:1 AV block as compared with patients with normal ECG results. 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 to 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 bpm) 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, PVC decrease significantly when receiving TCA, because of quinidine-like antiarrhythmic effects of TCA. This issue must be considered when patients are taking a type 1 antiarrhythmic, because the dosage may need to be changed. Patients receiving antiarrhythmics will require close ECG monitoring (65).

2.8.4.3. Dermatologic

Cutaneous vasculitis, urticaria, and photosensitivity are the dermatological ADR that have been reported. Usually occurring within the first 2 months of therapy, the skin reactions usually are harmless and rarely require discontinuation of therapy (65).

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 very rare, has a 10 to 20% mortality rate. It occurs most often in the second month of therapy, usually in elderly, female patients. Routine periodic WBC monitoring is not recommended (65).

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 patient becomes 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).

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. Because weight gain can result in potentially serious compliance problems, SSRI may be reasonable options because of a lesser extent of weight gain associated with their use (65).

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 TCA 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. TCA 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 TCA responsible for causing a disturbance in sexual behavior. The problems are reversible after decreasing the dose or discontinuing the drug. Drugs with cholinergic action such as 20 mg bethanecol orally 1 to 2 hours before bedtime seem to correct erectile and ejaculatory impairment (65).

2.8.4.8. TCA/MAOI Combination Therapy

A 14-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 used 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 used, if this combination is used, it is recommended that all antidepressants be discontinued, 5 to 10 days for TCA and 14 days for MAOI, before the combination is started, and that, preferably, 150 mg/day amitriptyline and isocarboxazid be administered simultaneously at conservative doses (65).

2.9. Monoamine Oxidase Inhibitors

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 MAOI than TCA. 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). MAOI have also been found more effective than imipramine in treating dysthymia in two controlled trials.

The theory that MAOI 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 used 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 MAOI

are less effective than other agents. Combined results of five studies concluded the MAOI 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-hr patch, is approved for the treatment of MDD in adults. Efficacy was established by a 6-week and 8-week RCT that established that patch doses of 6, 9, 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).

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 the 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 6 weeks. Two weeks are required before the maximum inhibitory effect of 30 mg/day phenelzine is reached, whereas 4weeks are required for a 60 mg/day dose. It is estimated that 0.7 mg/kg/day tranylcypromine is equivalent to 1.0 mg/kg/day phenelzine. When switching a patient from one MAOI to another antidepressant, including tranylcypromine, a 14-day "washout" period is advisable because of the potential risk of a hypertensive crisis and SS (65). When switching from one MAOI to another (besides tranylcypromine), at least a 1-week washout interval is advised (262). A summary of the usually recommended antidepressant doses is presented in Table 34.3.

2.9.3. Adverse Effects

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 TCA 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 4 weeks and then seem to decrease in intensity. Patients older than 50 years are more likely to experience declines in standing and sitting blood pressure than are younger patients. Initially, during the first 6 weeks of treatment, phenelzine will produce a decrease in systolic and diastolic pressures. However, patients on chronic MAOI therapy for months to years will have their sitting diastolic and systolic pressures increase significantly during the first 2 hours after ingestion of the dose, after which the levels 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 MAOI 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 MAOI 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.

2.9.3.2. Neurologic

Neurologic side effects occur rarely but usually include ataxia, tremor, hyperreflexia, paresthesias, and seizures, possibly as a result of a pyridoxine deficiency. Pyridoxine, at doses of 150 to 300 mg/day for several weeks reverses the paresthesias (263).

2.9.3.3. Withdrawal Reactions

The abrupt discontinuation of a MAOI can result in withdrawal symptoms, but only rarely. The four cases reported are characterized by REM rebound producing disturbed sleep and nightmares, hallucinations, and delirium. We do not recommend routine tapering MAOI because of the infrequency of the withdrawal reactions.

2.10. CNS Stimulants

Although substantial anecdotal literature exists suggesting that CNS stimulants may have some usefulness 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 that 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 30 mg/day methylphenidate for 3 weeks in poststroke 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 to 78% (265).

Fewer ADR are reported with the stimulants than the TCA. 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 decreasing order of frequency, include blood pressure changes, dysrhythmias, and tremor.

3. Mania

Mood stabilizers are used 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 used. 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.

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 MDD. 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).

3.1.1. Efficacy

3.1.1.1. Mania

In the initial treatment of an acute manic episode, a 3-week trial of lithium is recommended. The onset of action of lithium is often delayed 1 to 2 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 seem to respond similarly, although some patients may not tolerate typical antimanic lithium levels (272).

Lithium has been compared with 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 3 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 3-week treatment period compared with patients receiving a typical antipsychotic alone (273). In appropriate doses ($\geq$1,800 mg/day or $\geq$0.8 mEq/L), lithium produces marked improvement or remission in at least 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 an 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 (800–1,000 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 plus 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 plus haloperidol combination produced slightly greater symptom control than haloperidol alone (81). The SGA, risperidone (3.8 mg/day), was compared with 6.2 mg/day haloperidol 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 study concluded that 584 mg/day quetiapine combined with the mood stabilizers, lithium or valproate, was more effective than mood stabilizers alone, and the second study concluded that 492 mg/day quetiapine 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 because of nonresponse, whereas more patients dropped out of the haloperidol group because of ADR. After manic symptoms resolve, an attempt should be made to taper the benzodiazepine (usually over a week), and then discontinue.

3.1.1.2. Major Depressive Disorder

Sixty to 80% 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 3 weeks, but may take as long as 6 weeks. A therapeutic trial is considered 4 to 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, because only 30 to 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.

3.1.1.3. Continuation and Maintenance Treatment

Continuation treatment consists of uninterrupted pharmacologic management for 4 to 6 months after the acute episode is resolved, and is used to prevent relapse (exacerbation of current episode). Maintenance treatment is geared toward 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 2- to 4-week period significantly reduces the chance for relapse (283), which is especially important because abrupt discontinuation may lead to a rapid return of manic symptoms in some patients (284). Conservative recommendations for discontinuation would be a 4-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 to 6 months after symptom resolution (285). If lithium is used to treat depressive episodes, it should be continued at antimanic plasma levels for 4 to 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 lithium was 32%, compared with 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 with 5 years of previous episode (286). After first-episode mania, it is generally recommended to continue lithium for additional 3 to 6 months (after acute response) and then discontinue the drug. However, there may be situations in which maintenance treatment may be desired after 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 TCA (267). The 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 1 year (288).

The estimated suicide rate for patients hospitalized with unipolar and bipolar affective disorder ranges from 8 to 20% (289). A substantial body of data now suggests that lithium maintenance therapy decreases the risk of suicide in this patient population (290).

3.1.2. Dosing

3.1.2.1. Acute Mania

The generally recommended therapeutic range for lithium is 0.9 to 1.4 mEq/L. Patients with levels greater than 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 to 10 days after the beginning of treatment, depending on how quickly the lithium dose reaches the therapeutic range. Acutely manic patients tolerate and require higher lithium doses because of their increased lithium clearances. The initial doses are not tolerated once the manic episode begins to abate because 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

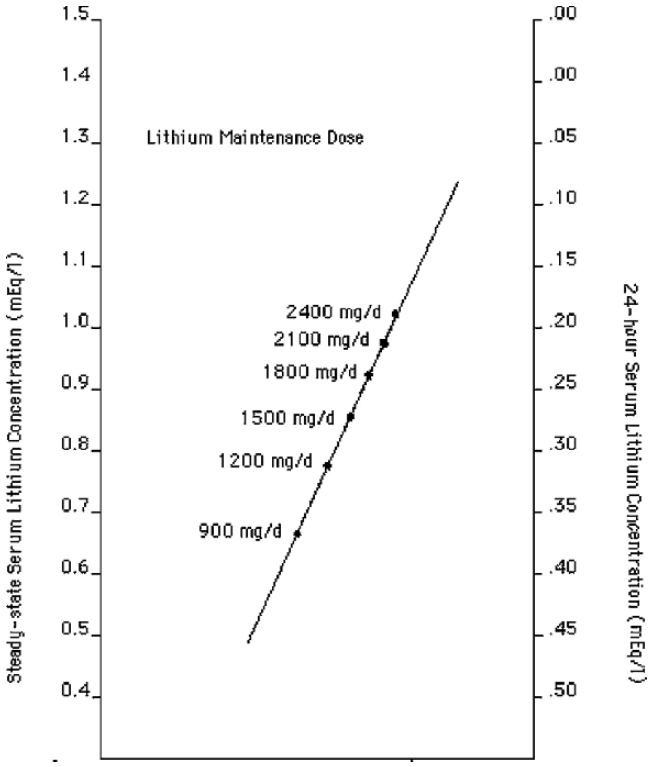

FIGURE 34.1. Lithium dosing nomogram for predicting steady-state serum concentrations for 900 to 2,400 mg/day maintenance doses after a 1,200-mg lithium carbonate test dose and then measuring the 24-hour serum lithium concentration (522).

manic hyperactivity begins to resolve. A summary of the usually recommended mood stabilizer doses is presented in Table 34.4.

3.1.2.2. Major Depression

The target lithium level for acute treatment of MDD is 0.9 to 1.4 mEq/L (267).

3.1.2.3. Continuation Treatment

The recommended lithium concentration for continuation treatment is 0.9 to 1.4 mEq/L (267).

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 concentrations between 0.45 and 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).

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 older than the age of 65 years should have levels drawn every 6 months, whereas younger patients should have levels drawn every 6 to 12 months, assuming that 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 2 weeks for several months to detect any changes in clearance. There is no universally accepted consensus recommendation for lithium level monitoring in the stable outpatient population. After approximately 4 months, it is recommended to switch the patient to single daily dosing. Patients generally can tolerate up to 1,500 mg/day as a single dose. Single daily dosing is preferred in patients because it results in less

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[b] 0.6–1.2 mEq/L[b]	Maintenance 900–1200[b] 0.45–0.6 mEq/L
Lamotrigine	Lamictal	25 (no inducer drugs)[a] 25 (added to valproate)[a] 50 (added to other inducers)	200 (no inducer drugs)[a] 100 (added to valproate)[a] 400 (added to other inducers)
Oxcarbazepine	Trileptal	750[b]	750–2400[b]
Valproic acid	Depakote Depakene	750[b]	750–4200[b]

[a] Inducer drugs include drugs such as barbiturates, carbamazepine, phenytoin, and St. John's Wort.
[b] Dose changes made by the editor.

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).

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 United States 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 a milligram-for-milligram 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.

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 1,200 mg/day will have a steady-state concentration of 1.50 mEq/L if the dose is increased to 1,800 mg/day, whereas, if the dose is decreased to 600 mg/day, the steady-state concentration should be 0.50 mEq/L.

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 to 40%, dependent on 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%; dermatitides, 3%; and muscle weakness, 1.6% (293). It is estimated that 60 to 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 to 0.6 mEq/L will significantly reduce the amount of patients who experience ADR (267, 285).

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 may be unrecognized as lithium related. CNS-compromised patients (e.g., those with seizure disorders or schizophrenia) may be predisposed to this ADR, thus, in this 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).

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).

3.1.3.3. Gastrointestinal

Gastrointestinal 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 using 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 using the more quickly absorbed liquid lithium citrate product formulation (65).

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 1 week and is reversible within 1 to 2 weeks. The elevated platelet counts may require 2 to 4 months to normalize (65).

3.1.3.5. Endocrine

Weight gains of greater than 10 pounds are estimated to occur in 11 to 64% of patients taking lithium. Studies report weight gain ranging from 3 to 28 kg, with an average of 8.5 kg during 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 to 23%. Patients developing hypothyroidism are most commonly women older than 40 years of age. Treatment may not be necessary because 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 that lowering the dose may reverse the hypothyroid symptoms. Goiter and the hypothyroid state can be reversed with thyroid supplementation. Preexisting hypothyroidism is not an absolute contraindication to lithium treatment. Lithium can increase serum calcium, reduce serum phosphorous, and increase parathyroid hormone (PTH) in approximately 10 to 15% of patients. Complications of primary hyperparathyroidism do not occur, although 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).

3.1.3.6. Neuromuscular

Lithium-induced tremor is reported to occur in 4 to 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, 30 to 80 mg/day propranolol, is an alternative. Muscle weakness, a transient side effect, seems to be dose related and disappears with reduction or discontinuation of lithium (65).

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 after the discontinuation of the lithium therapy. Severe cases can result in serious fluid and electrolyte disturbances that could result in toxicity. Because 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 and 0.8 mEq/L will minimize this ADR. The use of single daily dosing may help to prevent polyuria. The diuretics, 50 mg/day hydrochlorothiazide or 10 to 20 mg/day amiloride, have been used. Thiazides may reduce lithium clearance and produce hypokalemia, whereas 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:

$$Cl_{Cr} = (140 - \text{age}) \times (\text{kilograms body weight})/(72) \times (\text{fasting serum creatinine})$$

There are three important points to remember regarding the use of the above equation to insure its accuracy: 1) the calculated Cl should be reduced by 15% in women; 2) a correction to lean or ideal body weight is necessary in excessively obese, edematous 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 to 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.

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 levels greater than 2 mEq/L.

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 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 reintroduction 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 (301).

Lithium is excreted in the breast milk at a concentration approximately 40 to 50% that of the mother's serum concentration. Infants may be at increased risk for lithium toxicity. Therefore, the American Academy of Pediatrics considers lithium to be contraindicated during breast feeding (302).

3.2. Valproic Acid

3.2.1. Efficacy

Valproic acid received FDA approval for the treatment of acute mania in 1995. 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).

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, multicenter study comparing lithium with valproate reported that more than 50% of both patient groups exhibited a greater than 50% reduction in symptoms of mania (271) However, more than 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 because 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 MDD, but one unpublished report did not differ from placebo in partial response rates (266).

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 approximately 2 to 4 hours. Most patients can be treated with a total daily dose of 1,000 to 1,500 mg. 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 to 125 μg/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 3 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.

3.2.2.1. Dosage Forms

Divalproex is available in two oral forms: the enteric-coated divalproex, and an extended-release formulation of the enteric-coated divalproex. Bioavailability for the extended-release formulation is 8 to 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 Sect. 3.2.3.5 Gastrointestinal ADR below). The 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. 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).

3.2.3. Adverse Effects

3.2.3.1. Cardiovascular

Edema, tachycardia, hypertension, palpitations, and hypotension have all been associated with the use of valproic acid (303).

3.2.3.2. Central Nervous System

The most common CNS effect of valproic acid is sedation, which 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).

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.

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).

3.2.3.5. Gastrointestinal

Gastrointestinal ADR 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.

3.2.3.6. Hepatic

Increases in hepatic transaminases have been reported in 2 to 44% of patients (306). With discontinuation, dose reduction, or continuation, the enzymes will return to baseline values. Baseline liver function tests are recommended before initiation. One group of authors recommended that affective disorder patients should have these tests performed monthly for the first several months and then every 6 to 24 months thereafter. Potentially fatal idiosyncratic but rare (1 per 37,000 patients) 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 younger than 10 years old (65).

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 the 17th through 30th days of gestation should consult their clinician regarding prenatal testing (313). No adverse reactions from valproate exposure in the nursing infant have been reported (313). The medication is compatible with breastfeeding (314). Because valproic acid is excreted in the breast milk, breast feeding is not recommended.

3.3. Carbamazepine

The extended-release form of carbamazepine is FDA approved 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).

3.3.1. Efficacy

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

3 weeks in length. Carbamazepine has comparable efficacy with lithium and chlorpromazine (316–319). Compared with 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).

3.3.1.2. Major Depressive Disorder

Carbamazepine is not effective in the treatment of depression (322).

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, classic nondelusional bipolar patients had a lower rehospitalization rate with lithium than with carbamazepine prophylaxis; whereas there was no difference in effectiveness among the nonclassic 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).

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 2 weeks at this dose, the dose may be increased because of 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 2 weeks. Because 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 to 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 1 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 μg/ml might be tried. A repeat carbamazepine level might be obtained 3 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 greater than 12 μg/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.

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.

3.3.3. Adverse Effects

The chemical structure of carbamazepine resembles a TCA. Thus, most of its ADR profile resembles that of a TCA.

3.3.3.1. Cardiac

Carbamazepine can suppress both AV conduction and ventricular automaticity. However, significant ECG changes have only been reported in patients with preexisting 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).

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 or dopamine blockade can occur 2 to 3 weeks after the start of therapy (65).

3.3.3.3. Dermatologic

Carbamazepine-induced dermatologic reactions occur in 2 to 12% of patients (330,331). The reactions occur within the first 5 months of treatment. They include rashes with or without edema, systemic lupus erythematosus, 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).

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).

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.

3.3.3.6. Hematologic

A transient mild leukopenia occurs in approximately 10% of patients after the start of therapy but it normally resolves within the first 4 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 CBC results are in the middle to upper range, no further monitoring is recommended; 2) if baseline CBC results are in the low–normal or below normal range, the CBC should be measured every 2 weeks for the next 1 to 3 months; and 3) if the white count falls below 3,000 cells/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 their physician at the first sign of an infection, fever, fatigue, ecchymosis, and/or mucous membrane bleeding (333).

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).

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).

3.3.3.9. Teratogenicity and Lactation

Carbamazepine is a categorized as a pregnancy risk factor D drug. A study using 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 μg/ml (338). The milk-to-plasma ratio of carbamazepine ranges from 0.24 to 0.69 (313). The drug is compatible with breast feeding (314).

3.4. Lamotrigine

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).

3.4.2. Efficacy

3.4.2.1. 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.

3.4.2.2. 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 with placebo, up to 400 mg/day lamotrigine roughly doubled the time between affective episodes (343, 344).

3.4.2.3. 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).

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 benefits 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; and 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; and week 6: 100 mg/day (target dose). If lamotrigine is added to one of the above enzyme-inducing drugs (except for 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 during a 2-week period, in equal weekly increments. For patients discontinuing carbamazepine or any CYP450 enzyme-inducing agents, the dose of lamotrigine should remain constant for the first week and then should be decreased by half during 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 approximately 50% per week during at least 2 weeks, unless concerns for the patient's safety require a more rapid withdrawal (346).

3.4.4. Adverse Effects

Lamotrigine at a dose of 100 to 400 mg/day seems 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.

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 coadministration of lamotrigine with valproate, or 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).

3.5. Oxcarbazepine

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 with 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.

4. Anxiety Disorders

The anxiety disorders included in this discussion are generalized anxiety disorder (GAD), panic disorder (PD), obsessive–compulsive disorder (OCD), posttraumatic 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 of the anxiety disorders.

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).

4.1.1. Efficacy

4.1.1.1. Generalized Anxiety Disorder

A review of controlled studies noted numerous problems that make determination of an overall conclusion regarding BZD efficacy in GAD difficult (351). Approximately 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 to 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).

4.1.1.2. Panic Disorder

The results from controlled trials conducted with more than 1,700 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 an SSRI (374,375). The results of these studies have suggested that the combination of a BZD 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 (2.5 years) reported that the drugs maintained their efficacy and were well tolerated (376). A meta-analysis of treatment of panic disorder concluded that BZD maintained effectiveness when used for long-term treatment, but none of the studies cited were controlled (377).

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 BZD 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).

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).

4.1.1.5. Posttraumatic Stress Disorder

A controlled trial found alprazolam producing modest improvement in anxiety symptoms, but not the intrusion or avoidance symptoms of PTSD (385).

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 2 mg/day alprazolam, 55 mg/day chlordiazepoxide, 22 mg/day clorazepate, 14 mg/day diazepam, and 10 mg/day lorazepam (351). These doses may be higher than in clinical practice, because they were used in studies investigating maximum short-term benefit. In GAD, diazepam has been shown to be effective

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	10	10–300
Clonazepam	Klonopin	0.25	0.25–4.0
Diazepam	Valium	4	4–40
Lorazepam	Ativan	1*	1–4*
Oxazepam	Serax	15*	15–120*
Nonbenzodiazepine			
Chloral hydrate	Somnote	500	500–1000

*Editor's changes.

in the standard recommended daily dose range of 5 to 40 mg. The median dose used was 30 mg/day (388). Treatment with alprazolam is initiated with 0.25 or 0.5 mg, two to three times daily. Dosages may be increased every several days. Most patients require 3 to 6 mg/day to respond, but 10 mg/day may be required. Duration of initial treatment of 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 BZD 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 6 mg/day alprazolam, 55 mg/day chlordiazepoxide, 29 mg/day clorazepate, 30 mg/day diazepam, 4 mg/day lorazepam, and 3 mg/day clonazepam (371). These doses reflect an attempt to achieve maximum benefit in the short term and may be higher than those used in clinical practice. In panic disorder, the recommended daily dose range for diazepam is 5 to 40 mg; the median effective dose is 30 mg/day. Treatment with alprazolam is initiated with 0.25 or 0.5 mg two to three times daily (363). Dosages may be increased every several days. Most patients require 3 to 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 twice daily.

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 very long, the duration of action of a single dose is very short because high fat solubility 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 oral dose of 2.5 mg lorazepam 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 10 mg diazepam lasted 5 to 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 on 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 to 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 to 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 BZD 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 BZD is large, the choice of the particular BZD is not as important as is gradual dose titration and close monitoring (396, 397).

BZD can produce greater effects on the CNS in the elderly than in younger patients. This is caused partly by increased target-organ sensitivity to BZD and partly by changes in drug disposition in the elderly (399). All BZD, given in repeated doses, will accumulate to some degree and may produce ADR (400). The BZD 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 BZD 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-lives are not greatly changed in the elderly, the dosage administration schedule can be more similar to that in younger patients.

4.1.3. Adverse Effects

BZD have few pharmacologic effects outside the 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 less than 1% (401).

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 to 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 BZD 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 weeks or longer will experience withdrawal symptoms on 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 BZD 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 regarding driving and operating machinery, especially during the first few weeks of treatment (410).

Anterograde amnesia may occur with all BZD (411). Parenteral administration has been most commonly reported to produce this effect, but it is also reported with oral use. BZD exert their primary effect in impairing acquisition of new information, but do not seem to affect a person's ability to retain acquired information. The clinical effect of BZD 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.

Similar to ethanol and barbiturates, BZD have been reported to produce paradoxical excitement, disinhibition, hostility, rage, and even violent, destructive behavior. These ADR 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).

4.1.3.2. Respiratory

BZD are relatively benign as compared with other anxiolytic/hypnotics in their effects on respiration. Even though overdoses with BZD are frequent, serious sequelae are rare because of minimal respiratory depressant effects. However, in patients with compromised pulmonary function, BZD may produce clinically significant respiratory depressant effects. All anxiolytic/hypnotics should be used with caution in patients with reduced pulmonary function (410).

4.2. Antidepressants

4.2.1. Indications

Most of the antidepressant classes marketed have been studied for their potential to treat anxiety disorders.

4.2.2. Efficacy

4.2.2.1. SSRI and Venlafaxine

Generalized Anxiety Disorder. 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). Escitalopram and 50 mg/day sertraline and are similarly effective (417, 418). Extended-release venlafaxine has also been FDA approved 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 SSRI to other antidepressants when it found effect sizes of other antidepressants equivalent to the effect sizes of SSRI in acute treatment of panic disorder (421). Paroxetine was the first SSRI to be FDA approved for panic disorder, based on large multicenter 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); 20 mg/day fluoxetine, 125 mg/day sertraline, 20 to 30 mg/day citalopram, and venlafaxine are also effective (425–430).

Social Anxiety Disorder or Social Phobia. Sertraline and paroxetine are both FDA approved for the treatment of social anxiety disorder. Paroxetine has been studied more than the other SSRI agents. The response rate ranged from 55 to 66% (431, 432). Escitalopram, fluvoxamine, and venlafaxine have also been found effective (433–437). Bupropion and maprotiline were ineffective (438, 439).

Posttraumatic Stress Disorder. Agents in the SSRI and serotonin–norepinephrine reuptake inhibitor (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 approved for the treatment of PTSD. The studies noted improvement in all PTSD symptom clusters (intrusive recollections, avoidant/numbing symptoms, and hyperarousal), although effect sizes were modest (sertraline, 0.3–0.4; paroxetine, 0.5), and higher doses did not show additional benefit as compared with 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).

4.2.2.2. Tricyclic Antidepressants

Generalized Anxiety Disorder. 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 with 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, whereas imipramine predominantly affected the psychic component (388).

Panic Disorder. The use of TCA 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, 25–225 mg/day) in four studies (456–458).

Posttraumatic Stress Disorder. One small study with amitriptyline and one small study with imipramine found TCA to have modest effects on PTSD symptoms on veterans (459, 460). A 4-week trial of desipramine, however, did not demonstrate an effect on symptoms of PTSD. None of the TCA alleviated avoidance and numbing symptoms (445,461).

4.2.2.3. Monoamine Oxidase Inhibitors

The pharmacologic management of panic disorder and agoraphobia with panic attacks was originally investigated in the early 1960s with MAOI and with TCA (378, 462, 463).

Panic Disorder. Controlled trials (five trials with phenelzine) concluded that MAOI are effective in between 65 and 70% of patients with panic disorder (464–467). The overall response rate with MAOI was slightly less than for TCA, but this may have been due to limitations such as low doses of MAOI used, small sample sizes, and mixed groups of patients. MAOI are rarely used because of 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 because of the reasons listed previously.

Posttraumatic 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. Although not well studied, combination treatment with various agents has been reported to succeed when individual drugs fail (464).

4.2.3. Dosing

The time to response was 2 to 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 greater than 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 to 25 mg/day, which can be increased to 100 to 200 mg/day during a 2- to 4-week period. If a response is not seen in 2 to 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 to 12 months with pharmacologic management (455). Therefore, after 6 to 12 months of successful treatment, it is reasonable to consider discontinuing medications (472). However, regardless of whether the patient has been successfully treated, approximately 50 to 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 during 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 to 6 months.

4.2.4. Adverse Effects

See antidepressant adverse effects.

4.3. Buspirone

4.3.1. Efficacy

Buspirone is the first non-BZD anxiolytic to be introduced in the United States. 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 panic disorder (368, 476).

4.3.2. Dosing

The usual anxiolytic dose is 15 to 45 mg/day. The initial starting dose is 15 mg/day divided two to three 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.

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 greater than 20 mg/day. Dizziness was reported to occur 30 to 60 minutes after buspirone was administered, especially when subjects were walking or standing.

Dysphoria has been reported, primarily with doses greater than 30 mg/day. Initial studies indicated that buspirone less than 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.

4.4. Beta-Adrenergic Blocking Drugs

4.4.1. Efficacy

Of the beta-adrenergic receptor blocking agents available in the United States, propranolol is the most extensively studied in the management of anxiety. It is not approved by the 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 seem to be effective in the treatment of acute situational anxiety (481). The drugs seem 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).

4.4.2. Dosing

Forty to 80 mg propranolol has been used successfully in acute situational anxiety and for social phobia (378). The dose should be administered 1 to 2 hours before the stressful event.

5. Obsessive–Compulsive Disorder

Most of the medications shown to have efficacy in OCD are serotonin agonists. With current treatment options, a 10-week course of drug treatment will generally result in 40 to 60% of the OCD patients experiencing approximately a 20 to 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. Because of 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).

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 with treatment of MDD. For example, both paroxetine and fluoxetine had to be given at 40 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).

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 multicenter trial showed a 40% reduction in OCD symptom ratings in patients treated with clomipramine compared with a minimal reduction in symptoms for patients treated with placebo (498).

5.2.1. Efficacy

Clomipramine is a specific serotonin reuptake blocker, although its metabolite, desmethylclomipramine, has effects on blocking norepinephrine reuptake.

5.2.2. Dosing

The initial dose is 25 mg/day clomipramine administered as a single dose at bedtime. The dose should be gradually increased over several days to 2 weeks, as determined by side effects, to a minimum dose of 150 mg/day. Patients who show no response to 150 mg/day after 4 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 2 or 3 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.

5.2.3. Adverse Effects

Clomipramine side effects are similar in severity and nature to those of TCA, 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 patients) developed anorgasmia, usually within the first few days of clomipramine initiation (499).

6. Dementia

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.

6.1.1. Tacrine

Tacrine produced a mean 4 to 6% advantage over placebo in patient studies longer 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. Because of the high risk of significantly elevated liver function test results, serum transaminase levels should be performed every other week from at least week 4 to week 16, and then every 3 months thereafter.

6.1.2. Donepezil

Studies of patients with mild to moderate DAT showed that donepezil produced a 4 to 6% improvement in cognitive and global change scales when compared with placebo (501, 502). Frequently reported ADR were mainly gastrointestinal 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 mold to moderately severe DAT (504). Donepezil was shown to decrease caregiver time as well as lower the level of caregiver stress caused by the slowing decline of activities of daily living (ADL) in patients with moderate to severe Alzheimer's disease 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 (505, 506). Donepezil is available as 5 and 10 mg tablets. Dosing should start at 5 mg daily, and the target dose is 5 to 10 mg/day. The most common adverse reactions reported include nausea, diarrhea, vomiting, muscle cramps, fatigue, and anorexia.

6.1.3. Rivastigmine

Rivastigmine, marketed in 2000 for the treatment of Alzheimer's disease, is administered once daily. Two controlled trials showed that rivastigmine produced 25 to 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 to 12 mg daily because of cholinergic ADR. Rivastigmine should be initiated at 1.5 mg twice daily, and may be increased every 2 weeks to a maximum of 6 mg twice daily. The most common ADR

include nausea (47%), vomiting (31%), anorexia (17%), and weight loss (18–26%).

6.1.4. Galantamine

Galantamine is an acetylcholinesterase inhibitor that also acts as a modulator at nicotinic cholinergic receptor sites. In a controlled trial of patients with DAT administered placebo or 18, 24, or 36 mg/day galantamine for 3 months, patients treated with 24 mg/day galantamine had better cognitive outcomes than patients given 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 to 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.

6.2. NMDA Receptor Antagonists

6.2.1. Memantine

Memantine, a NMDA glutamate receptor antagonist, is the only agent currently 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, adding memantine was proven to save caregiver time, and improve cognition, ADL, global outcome, and behavior (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.

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 that 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 (CVE) 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).

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 BZD receptor agonists (BZRA) marketed as hypnotics (e.g., flurazepam, temazepam, quazepam, estazolam, triazolam, zolpidem, and zaleplon) are the most useful hypnotics available to the clinician. The term BZRA refers to BZD in addition to the three newest hypnotics (zolpidem, zaleplon, and eszopiclone). Zolpidem, zaleplon, and eszopiclone are not BZD by chemical structure (zolpidem is an imidazopyridine, zaleplon a pyrazolopyrimidine, and eszopiclone a pyrrolopyrazine), but are pharmacologically active at the BZD receptor. Ramelteon, a melatonin receptor agonist, is hypothesized to be more effective than melatonin for sleep.

All of 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 not be used 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 after a high fat content meal. Because of its short duration of action, it can be used as late as 4 hours before 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 seem 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 younger than 65 years old (521).

A summary of the usually recommended anxiolytic doses is presented in Table 34.6.

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[a]	7.5–30[a]
Triazolam	Halcion	0.125	0.125–0.25
Nonbenzodiazepine 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

[a] Dose changes made by the editor.

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35
Cognitive and Behavioral Therapies

Edward S. Friedman, MD and Michael E. Thase, MD

Abstract For longer than 40 years, the cognitive and behavioral therapies have evolved as alternatives to more traditional nondirective and insight-oriented modes of psychotherapy (1). The 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 the opportunity to practice therapeutic skills and to generalize positive behaviors outside of the therapy hour. Third, treatment is based on the objective assessment of psychiatric symptoms and selection of therapeutic strategies derives logically from such assessments. Fourth, the therapeutic methods used are generally structured, directive, and characterized by a high level of therapist activity. Fifth, for most disorders, the cognitive and behavioral therapies are time-limited interventions. Sixth, these therapies are based on empirical evidence that validates and guides the choice of therapeutic techniques: learning theory (i.e., classical, operant, and observational models of learning) and the principles of cognitive psychology.

Keywords Behavioral · Cognitive · Learning theory · Psychoeducation · Psychotherapy

1. Cognitive Model

The proposition that cognition is the primary determinant of emotion and behavior dates back to the writings of the Greek Stoic philosophers (2). However, the work of Aaron T. Beck has been the greatest impetus for the modern development of cognitive therapy (Beck uses the term "cognitive therapy," but, for simplicity's sake, in this chapter, we have adopted the more widely used term, "cognitive–behavioral therapy [CBT]") (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 reviews the philosophical and theoretical assumptions of the cognitive model. Additional contributions from cognitive psychologists, behavioral therapists, and other clinical practitioners have subsequently been incorporated into the cognitive model (8).

In the 1960s, as Beck began to formulate his theories, the predominant treatment approach was psychoanalytically oriented therapy. Freud conceived of depression as resulting from anger turned inward (9). However, Beck could not find evidence for this hypothesis, instead noting stereotypical patterns of pessimism, self-criticism, and distorted information processing in depressed patients (3). This early work led to development of a cognitive model of depression (4), the description of specific treatment interventions, and a substantial research effort to study cognitive functioning and treatment outcome in a variety of disorders (8, 10).

Figure 35.1 displays 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 occur, as shown in Table 35.1. The individual's behavioral responses to stimuli and thoughts are viewed as both a product and a cause of maladaptive cognitions. Thus, treatment interventions may be targeted at any or all components of the model.

Of course, many other factors are involved in 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 for synthesizing cognitive and neurobiological factors in a combined therapy approach. Contemporary psychiatric research is striving to

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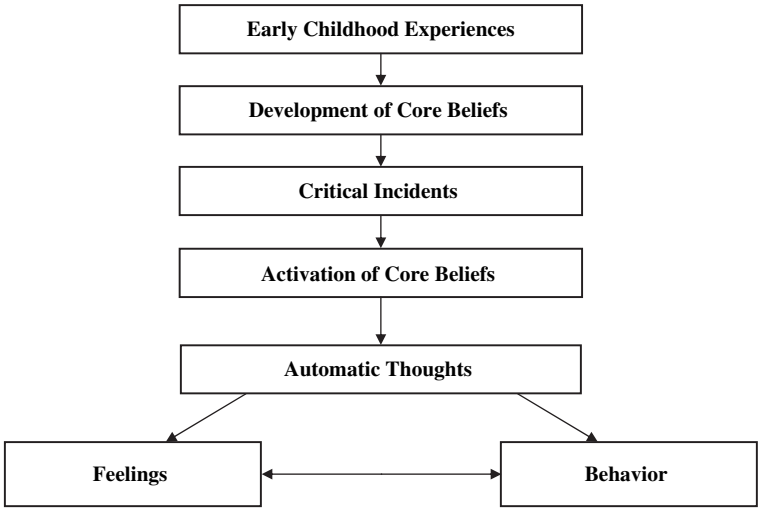

FIGURE 35.1. A schematic representation of the cognitive model.

understand how best to combine and/or sequence CBT and pharmacotherapy, and relate CBT technique to new understandings in cognitive neuroscience. Nevertheless, the working model in Fig. 35.1 can be used as a practical template to guide the therapist's case formulation and interventions.

1.1. Automatic Thoughts and Schemas

The CBT model conceptualizes many psychiatric disorders to be the result of dysfunctional information processing at two major levels of cognition—automatic negative thoughts (ANTs) and schemas (relatively stable cognitive patterns) (6, 12, 13). Automatic negative thoughts are stream-of-consciousness thoughts that arise spontaneously or in response to some prompt or stimulus. They may be triggered by affective arousal (i.e., anger, anxiety, or sadness), or, conversely, affective shifts are generally accompanied by automatic negative thoughts (14). These thoughts enter into awareness and are generally accepted as believable—they have emotional validity. Although we all experience automatic thoughts, in depression, anxiety, and other psychiatric disorders, the thoughts are distinguished by their greater

TABLE 35.1. The Dysfunctional Thought Record, an example.

Dysfunctional thought record				
Situation/behavior	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.	Personalization	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.

Note—her parents were supportive of her getting help.

intensity and frequency. LeFebvre (15) and Beck (5) coined the term cognitive triad to describe the content areas of automatic negative thoughts. Typically, automatic negative thoughts are about oneself, one's world (i.e., significant others or people in general), and one's future. For CBT practitioners, the thematic content of automatic negative thoughts can be used to reveal deeper levels of cognition: beliefs, rules, and schemas. Patients can be taught to examine their beliefs and the operational rules that produce them. Although patients are not fully aware of their schemas, these cognitions are usually accessible through the questioning techniques used in CBT (16).

Beck and coworkers (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 35.2. 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 such 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. Thus, people may be primed 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. However, the affective pathway is shorter, allowing activation 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 ones 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 wellbeing 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 one's 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, and 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 35.3. 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 use the rule: "If I am loved by others, then I am worthwhile." Such a rule might remain latent until activated by a life stress, for example, a romantic breakup. In such a situation, the vulnerable person experiences considerable emotional turmoil, whereas someone with a more resilient self-schema might be confident in their likelihood of having another relationship in the future, and they may only experience a limited period of sadness (23). Some schemas may 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 expe-

TABLE 35.2. 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 (black or white, absolutistic) thinking	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," "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 reference (10).

TABLE 35.3. Proposed maladaptive schemas.

Autonomy	
Dependence	The belief that one is unable to function with 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) 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 maladaption 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 reference (17). Adapted from Young J: Schema-focused cognitive therapy for personality disorders. Unpublished manuscript, Cognitive Therapy Center of New York, 1987.

riences 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, and dampen hedonic capacity (11). As a consequence, the individual may develop the dysfunctional attitude "I am powerless to change my destiny," expressing helplessness and hopelessness—the cognitive correlates of chronicity.

In general, studies of people 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 also demonstrated elevated levels of dysfunctional attitudes, distorted attributions to 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. Theoretical assumptions and treatment strategies for CBT of many other conditions, including the eating disorders, substance abuse, personality disturbances, and psychoses, have been articulated. The reader is referred to publications on these topics for descriptions of how the cognitive model can be adapted for treatment of a wide variety of psychiatric disorders (20, 25–32). Specific applications of cognitive and behavioral treatment strategies are described later in the chapter.

1.2. Behavioral Model

Learning theory provides the foundation for the behavioral therapies and dates to the work of Pavlov (33) and Skinner (34). Since that time, much research on learning in animals has examined patterns of acquisition and maintenance of behavior. Abnormal or "neurotic" behaviors in animals could be 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). This suggested that behavioral approaches could also be applied to psychiatric illness. By the late 1950s, within academic clinical psychology, there was dissatisfaction with the medical and psychoanalytic models of psychopathological processes and treatment. Critical problems such as poor diagnostic reliability and the lack of evidence supporting the effectiveness of psychodynamic psychotherapy were recognized. The modern psychopharmacology revolution was still in its infancy and no alternative paradigm at the time 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, chronic mentally ill, patients. Counterconditioning treatment of anxiety disorders using 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, such as an individual's history, their inherent talents, and the adaptability of their response repertoire produce interindividual variability in stimulus–response relationships (8).

1.3. Selection of This Modality

Selection of CBT for an individual patient should be based on the appropriateness of CBT for the treatment situation. Relevant questions include: Is the patient psychotic? If so, are there specific target behaviors and has psychopharmacological treatment been optimized? Does the patient suffer from a disorder known to be responsive to CBT? Within groups of patients with potentially treatable disorders, other indicators of response include chronicity, severity, and comorbidity. A good general rule is that patients with acute, mild to moderately severe, mood and anxiety disorders are the best candidates for treatment with CBT alone (35). Patients with more chronic, severe, or complicated illnesses may be better candidates for combined treatment strategies than for CBT alone (36). McCullough (37) has developed a variant of CBT for chronic depression that has shown much promise alone and combined with antidepressant medication.

An outpatient trial of acute phase CBT for depression or anxiety typically ranges from 10 to 20 treatment sessions (10). Deterioration or noncompliance of the patient 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 the depressive disorder. We will discuss these phases of treatment in greater detail in section 1.6. During treatment of major depressive disorder and panic disorder, a majority of patients who will benefit from CBT will show a significant reduction in symptoms within 6 to 8 weeks of starting therapy (41). Moreover, those who show a late response to CBT (i.e., between weeks 12 and 16) may be at high risk for subsequent relapse (42).

1.4. Issues of Sex, Race, and Ethnicity

The cognitive and behavioral therapies seem equally effective for men and women and people of various races (43). As with other forms of psychotherapy, a productive CBT working alliance is based on mutual respect for individual differences (44). For some persons with sex, racial, or ethnically related issues, it may be useful to select therapists with special skills or experiences (e.g., therapists specializing in gay and lesbian issues or posttraumatic stress syndromes caused by rape or incest). It has been recommended that cognitive–behavioral therapists receive special training and supervision in methods of responding to sex, race, and ethnicity variations (44).

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). It is likely that multimedia programs will have an increasing 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 in examining and trying out new behaviors; 2) they are expected to do homework; 3) the outcome of therapy will be measured and strategies will be altered if they are not helping; 4) therapy will be focused on symptoms and social functioning and generally will be time limited in nature; and 5) the chances of success after treatment termination can be gauged by the patients' incorporation of the therapy into their day-to-day life.

1.6. Phases of Treatment

Most cognitive and behavioral therapies use a three-stage process. The initial phase includes clinical assessment, case formulation, establishment of a therapeutic relationship, socialization of the patient to therapy, psychoeducation, and introduction to treatment procedures. The middle stage involves the sequential application and mastery of cognitive and behavioral treatment strategies. The second stage ends when the patient has obtained the desired symptomatic outcome. The final phase of therapy is characterized by preparation for termination. Sessions are scheduled more widely apart to test the durability of treatment and to shift the responsibility for using therapeutic strategies from the therapist to the patient. Another goal of the third stage of treatment is relapse prevention. Strategies are reviewed that reduce vulnerability to stress or high-risk situations. This includes the identification of prodromal symptoms, the rehearsal of self-help procedures, and the establishment of guidelines for return to treatment (49). The failure to achieve a remission of depressive symptoms after 16 to 20 weeks of treatment 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 plan.

1.7. Intensity and Duration of Treatment

Outpatient CBT is normally conducted once or twice a week. In selected cases, three-times-weekly or even daily sessions may be useful, but the cost-effectiveness of such a labor-intensive 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. Many

programs blend individual and group therapies (29). In our experience, more frequent sessions are needed to overcome demoralization in severely ill patients (50).

In most cases, the duration of a course of CBT 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. Therapy should not be terminated until patients have achieved symptomatic remission. Ideally, at least two or three sessions are planned on an every-other-week basis in preparation for termination.

1.8. Augmentation of Therapy

It is not uncommon to add an appropriate form of pharmacotherapy for depressed patients undergoing CBT. In some cases, the neurobiological substrate of the illness may be too severely disturbed to be responsive to the CBT without concomitant pharmacotherapy (51). 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 only talk therapy.

There are no contraindications to combining CBT and pharmacotherapy (11). In fact, these modalities are highly compatible in theory and practice (36). As noted earlier, pharmacological stabilization is a prerequisite for CBT for some Axis I disorders (e.g., psychotic depressions, schizophrenia, and bipolar disorder). Combining pharmacotherapy and CBT requires a well-defined division of labor among providers, open lines of communication, and an explicit sense of collaboration. Treatment of patients with severe, refractory, or incapacitating mood and anxiety disorders may represent the best use of combined therapies (52). Other strategies used to enhance CBT include increasing the frequency of visits, switching emphasis (i.e., from a predominantly cognitive to behavioral focus or vice versa), or involving the spouse or significant others in the therapy. The last 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 for CBT (48, 55, 56). Greater availability of personal computers with multimedia capability and increased pressure to reduce the cost of treatment may make this form of therapy augmentation a more common practice in clinical settings.

1.9. Continuation and Maintenance Phase CBT

Because some patients do not completely achieve a remission of symptoms (a return to their premorbid well state) and because many patients experience depression as a recurring illness, there is a need for longer-term treatment methods for major depression (57). Furthermore, incomplete remission of depression leads to recurrence, and this conveys many adverse economic, interpersonal, and medical consequences (58). Failure to achieve a complete remission of the index episode by the sixth week of acute phase CBT is associated with a threefold to fivefold increase in the subsequent risk of relapse or recurrence. Thase and coworkers (42) have found that between 50 and 60% of CBT responders meet this criteria 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, and developmental), psychosocial (personality, interpersonal, and social), and cognitive (40). By identifying and modifying risks and vulnerabilities and learning more effective ways of managing mood symptoms, C-CT helps patients prevent relapse and recurrence.

Fava (59) has developed another interesting approach to reduce the risk of relapse, the sequencing of treatment depending on the degree of response after acute-phase therapy. He 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.

2. Efficacy of CBT

The cognitive and behavioral therapies are, as a class, the best-studied type of psychotherapy. Numerous research studies have demonstrated the efficacy for a variety of Axis I disorders (65).

2.1. Mood Disorders

Evidence for the efficacy of Beck's model of CBT for mood disorders comes from studies of outpatients with nonpsychotic major depressive disorder. CBT is an effective treatment of major depression compared with a waiting list control condition (35). Dating to an initial study by Rush and associates (66), one major research focus has been to establish the efficacy of CBT vis-á-vis antidepressant pharmacotherapy. At this time, eight controlled trials contrasting CBT and tricyclic antidepressants have been completed (37), as have a legion of studies using other designs and other comparison groups (35, 67). Only three 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, the ideal comparator for pharmacology efficacy studies (73) (Table 35.4).

There have been several large and important studies comparing 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, reported 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 seemed to be less effective than imipramine and slightly, although not statistically, less effective than interpersonal psychotherapy (IPT) (IPT is another time-limited, depression-focused, psychotherapy; IPT stresses here-and-now, interpersonal issues as the predominant focus of the therapy). When this same cohort was observed during the course of 18 months of follow-up, it was determined that there were no significant differences among any of the treatments with respect to the number of patients that recovered and remained well. However, in follow-up, CBT patients had the lowest rates of receiving some kind of treatment during the follow-up period and the lowest rates of relapse after 18 months, suggesting greater durability (74).

The acute-phase treatment findings of the TDCRP have raised questions regarding the suitability of CBT as a treatment of severe depression (75). Alternatively, the adequacy of CBT training and validity of the models of CBT (versus IPT) 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, multisite, randomized clinical trial using McCullough's CBT-based treatment, the Cognitive–Behavioral Analysis System for Psychotherapy (CBASP) (37, 82). In this study, CBASP demonstrated equal efficacy to the serotonin–norepinephrine reuptake inhibitor (SNRI), nefazodone, each being effective in 48% of cases; but the combination of the two treatments 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 version of CBT modified to specifically address the problems of severe and chronic depression. Additionally, in an interesting study using positron emission tomography (PET) scanning technology, Mayberg and colleagues found different regional metabolic changes in patients treated with paroxetine and CBT. Treatment with CBT is associated with characteristic metabolic changes in the frontal cortical regions of the brain; whereas medication treatment alters metabolism in the brainstem limbic regions (83, 84). These authors suggest that combining these two modalities may, therefore, synergistically improve

TABLE 35.4. Randomized controlled clinical trials comparing depression-focused psychotherapies and pharmacotherapy as acute-phase treatments of major depressive disorder.

Treatment study	N	Duration(weeks)	Comparison of efficacy
Rush et al., 1977 (66)	41	12	CT > imipramine
Rush and Watkins; 1981 (178)	39	12	Combined (tricyclic) [a] ≥ CT
Blackburn et al.; 1981 (78)	64	12	Combined = CT > tricyclic [a]; (general practice clinic setting)Combined [b] ≥ CT = tricyclic [a]; (psychiatric clinic setting)
Teasdale et al.; 1984 (179)	34	15	CT + TAU > TAU [c]
Murphy et al.; 1984 (79)	70	12	Combined = CT = nortriptyline
Beck et al.; 1985 (32)	33	12	Combined (amitriptyline) = CT
Beutler et al.; 1987 (180)	56	20	CT (group) + alprazolam > alprazolam alone
Covi and Lipman; 1987 (181)	70	14	Combined (imipramine) = CT (group)
Elkin et al.; 1989 (68)	239	16	CT < imipramine [d]
Hollon et al.; 1992 (80)	106	12	Combined [b] ≥ CT = imipramine
McKnight et al.; 1992 (182)	43	8	CT = amitriptyline [e]
Murphy et al.; 1995 (183)	37	16	CT = RT > desipramine
Blackburn and Moore; 1997 (63)	75	16	CT = antidepressants [a]
Jarrett et al.; 1999 (69)	108	10	CT = phenelzine > placebo
Keller et al.; 2000 (82)	681	12	Combined > CT = nefazodone
DeRubeis et al.; 2005 (70)	240	16	CT = antidepressant

CT, cognitive therapy; TAU, treatment as usual; RT, relaxation training; ">" indicates more efficacy; "≥" indicates at least as much efficacy and sometimes more; "=" indicates equal efficacy.

[a] This indicates doctor's choice of medication.

[b] Advantage of combined treatment was limited to selected measures.

[c] Treatment as usual (TAU) was provided by primary care physician.

[d] Imipramine was more rapidly effective than either form of psychotherapy. Also, imipramine was more effective than cognitive therapy in patients with Hamilton Rating Scale for Depression (Hamilton 1960) scores > 20.

[e] Melancholic and hypercortisolemic patients in both cells had significantly poorer outcomes. Reprinted with permission from reference (35).

treatment outcome. Similarly, in a meta-analysis of randomized controlled trials of combination CBT and medications (including tricyclics amitriptyline, clomipramine, nortriptyline, desipramine and nefazodone) versus medications alone, the authors found the likelihood of response to be almost twice as high in the combination group (36).

The 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 selective serotonin reuptake inhibitor (SSRI), citalopram. Subjects were randomized in the switch cell to sertraline (an SSRI), bupropionSR (a non-SSRI antidepressant), venlafaxineXR (a dual-acting agent), or CBT. In these treatment-refractory individuals, CBT was equally as effective as the medications in producing a remission of depressive symptoms (85).

Group CBT strategies for treatment of depression have also 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 a 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 CBT, alone or in combination. These authors found the group CBT to be 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 the functional impairments 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 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 indicated (89, 90), and such strategies have been described (91).

There is some evidence that CBT reduces the risk of relapse after termination of treatment (compared with patients withdrawn from antidepressants) (92–94). 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 a complete remission before ending treatment (42). The addition of CBT for relapse prevention in medication nonremitters has also been advocated (59).

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 significantly more rapid improvement (96, 98). Behavioral strategies emphasizing self-control and problem-solving skill, and increasing pleasurable activities have also been consistently found to be superior to a control condition consisting of being maintained on a waiting list; although these approaches have not yet been subjected to trials against antidepressants or other active treatments (35, 72).

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). CBT has also been shown in a randomized clinical trial to be an effective treatment for anxiety disorders in older adults at the end of therapy and over 12 months of follow-up. These authors included patients with a wide range of anxiety disorders to allow generalization of their findings to a greater "real-world" population (106).

For simple phobias, CBT treatments emphasizing progressive (graded) exposure, systematic desensitization, relaxation training, and homework assignments are considered the psychotherapeutic treatment of first choice (99, 102, 107).

Obsessive–compulsive disorder is also amenable to CBT interventions 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 (113), behavioral treatment of obsessive–compulsive disorder reduced glucose metabolism in the caudate nucleus (a putative site for obsessive–compulsive disorder) comparable to that observed in patients treated with pharmacotherapy.

Generalized anxiety disorder and social phobia are common conditions, often presenting with much 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 and a wait-list control group, results show a clear advantage for CBT over behavioral therapy. 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 generalized anxiety disorder, of CBT versus a nondirective supportive psychotherapy, found no significant differences between the treatments; although both reduced worry anxiety and depression (121). A meta-analysis of the extant controlled-outcome studies found that CBT for generalized anxiety disorder

produced significant improvement that is maintained for up to 1 year after treatment termination (122).

The comparative efficacy of cognitive and behavioral treatments and pharmacotherapy for panic disorder and agoraphobia has been intensively investigated (100, 101, 123–125). These treatments teach patients to disregard or de-emphasize 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 has 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 SSRI fluvoxamine was superior to CBT (131). However, in other studies, similar advantages favored CBT (124, 132, 133).

Even if it is 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 a significant reduction in patients' 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 it is used sequentially to reduce the risk of relapse after withdrawal of pharmacotherapy (137, 139). To date, 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 posttraumatic stress disorder. A review of controlled-outcome studies indicated that CBT is the psychological treatment of choice and that is more effective than eye movement desensitization and reprocessing (143).

2.3. Eating Disorders

The efficacy of CBT for bulimia nervosa has been demonstrated in many research studies (144–152). Reviews of controlled studies of CT 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 therapy-alone approach to bulimia (155). At follow-up assessment after 6 months of treatment, 69% of the subjects who received CBT reported no binge eating and purging as compared with 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 effect to antidepressant therapy (153, 154). There seems to be no added benefit to adding medication to CBT for patients with anorexia nervosa.

2.4. Bipolar Disorders

Two randomized control trials of CBT in patients with bipolar disorder have been reported. The first studied whether CBT improved lithium compliance at 6 and 12 months after treatment as compared with 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). The second study by Lam and colleagues examined the use of CBT to prevent relapse in bipolar patients who are taking mood-stabilizer medications. Modifications to 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 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 to 20 sessions and lasted 6 months, and outcomes were measured at 6- and 12-month points and compared with 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 they used significantly less neurologic medication (157). These benefits persisted after 2 years of naturalistic follow-up (158). These results support the findings of Scott and colleagues who also found a benefit for CBT treatment to prevent 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).

2.5. Other Disorders

Dialectical behavior therapy (DBT) is an effective treatment of borderline personality disorder. This modified form of CBT incorporates Zen practices of mindfulness and acceptance. DBT teaches patients to control parasuicidal, suicidal, and treatment-interfering behaviors, to improve coping skills, and to decrease mood lability and interpersonal conflict (25, 161,

162). In a recent 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 conclude that DBT seems to be uniquely effective in reducing suicide attempts (163). Cognitive and behavioral therapies have also been studied in substance abuse disorders and they tend to be more effective than standard counseling approaches only with patients with concomitant psychiatric illness (164–166). The directive methods used by cognitive–behavioral therapists may reduce resistance to change 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. Recently, 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 regarding sleep hygiene, sleep restriction, stimulus control, relaxation techniques, and cognitive interventions (168).

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 effect when CBT is combined with medication (173–177).

For example, Drury and coworkers (173, 174) observed greater improvement in positive symptoms in hospitalized patients who received CBT as opposed to those patients receiving nonspecific and supportive treatment. This research group also observed reduced time to recovery in patients treated with CBT. Sensky and coworkers (177) studied 90 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, 9 months after treatment, subjects who received CBT had significantly lower ratings on measures of positive and negative symptoms.

3. Conclusion

The cognitive and behavior therapies are based on well-articulated theories that have a strong empirical basis. These therapies emphasize objective assessments and use of directive interventions aimed at reducing symptomatic distress, enhancing interpersonal skills, and improving social and vocational 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 models for therapy by teaching patients how to recognize and modify their attitudinal vulnerabilities.

The cognitive and behavioral therapies are the best-studied psychological treatments of major depressive, panic, generalized anxiety, and obsessive–compulsive disorders. Overall, there is good evidence for the effectiveness of these interventions within these indications. Cognitive and behavioral therapies are being adapted for adjunctive use with pharmacotherapy for treatment of bipolar disorder and schizophrenia. There are no contraindications for use in combination with pharmacotherapy. The cognitive and behavioral therapies have become one of the standard psychosocial treatment approaches for mental disorders.

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36
Forensic Psychiatry

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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 Competency · Dangerousness · Expert witness · Forensic psychiatry · Insanity · Malingering · Malpractice

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).

In general, there are fundamental differences in the roles and responsibilities of a forensic psychiatrist when compared with 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 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 they experience posttraumatic 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 will generally pursue verification of alleged symptoms from outside sources and collateral informants. 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:

- Malingering
- Assessment of dangerousness
- Competency
- Criminal responsibility
- Expert witness testimony

2. Assessment of Malingering

According to the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) (2) and its text revision (DSM-IV-TR) (3), malingering is defined as "the intentional production of false or grossly exaggerated physical or psychological symptoms, motivated by external incentives such as avoiding military duty, avoiding work, obtaining financial compensation, evading criminal prosecution, or obtaining drugs." The DSM-IV-TR also notes that malingering is a condition not attributable to a mental disorder. The DSM-IV-TR recommends that malingering should be strongly suspected if any combination of the following are present:

1. Medicolegal context of presentation
2. Marked discrepancy between the person's claimed stress or disability and the objective findings

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3. Lack of cooperation during the diagnostic evaluation and in complying with the prescribed treatment regimen
4. The presence of antisocial personality disorder

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 to 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 to 33% of individuals psychiatrically assessed in personal injury evaluations are considered malingering (6, 7) and more than 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 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, they may do it very exactly, whereas the genuine schizophrenic patient will often wander off on a tangent. The psychotic patient'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. A malingerer's symptoms may fit no known diagnostic entity and may have 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 their 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 their crimes into a mental disease model.
8. Malingerers are 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 defendants are caught in contradictions, they 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.

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 best validated test for malingered psychosis (17, 18).

3. Assessment of Dangerousness

Dangerousness is not a psychiatric diagnosis like schizo phrenia. 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 release 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 (19). Fortunately, studies

that are more recent 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 (20).

When conducting a violence risk assessment, the clinician may find it helpful to divide the concept of dangerousness into five components. These five components include: 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 (21), lower socioeconomic status (22,23), and lower intelligence and mild mental retardation (24). Although men show much higher rates of violent offense than women in the general population among people with mental disorders (25), men and women do not significantly differ in their base rates of violent behavior (20, 26).

A history of violence is the single best predictor of future violent behavior (27). 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 they misperceive as a persecutor.

Drugs and alcohol are strongly associated with violent behavior (28, 29). The majority of persons involved in violent crimes are under the influence of alcohol or drugs at the time of their aggression (30). Stimulants, such as cocaine, crack, amphetamines, and PCP are of special concern.

Studies examining whether individuals with mental illness are more violent than individuals who are not mentally ill have yielded mixed results (21, 31–33). In a study of civilly committed psychiatric patients released into the community, most mentally ill individuals were not violent (34). 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 (35).

The presence of psychosis is of particular concern when evaluating a person's risk of future violence. 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 addition, paranoid persons in the community are more likely to be dangerous because they have greater access to weapons (36). A careful inquiry regarding hallucinations is required to determine whether their presence increases the person's risk to commit a violent act. Patients with schizophrenia are more likely to be violent if their hallucinations generate negative emotions (anger, anxiety, sadness) and if the patients have not developed successful strategies to cope with their voices (37). The presence of command hallucinations may increase the likelihood of behaving violently (28, 38), particularly if the voice is one familiar to the person (39) and if the person has delusional beliefs associated with the hallucinations (40).

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 (41, 42). Patients with mania show a high percentage of assaultive or threatening behavior, but serious violence itself is rare (36). Patients with mania most commonly exhibit violent behavior when they are restrained or have limits set on their behavior (43).

Brain injury or illness can also result in aggressive behavior. After a brain injury, formerly healthy individuals may become verbally and physically aggressive (44). 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 after 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 (45). Personality traits associated with violence include impulsivity (22), 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 (46).

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 (47). The clinician should also observe the patient for physical signs and symptoms of changes indicating incipient violence. Berg, Bell, and Tupin (48) 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-IV-TR personality disorders or traits, the clinician should also be familiar with the psychological construct known as psychopathy. The term psychopath was described by Cleckly (49) 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) (50) 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 generally and violence among adults (51).

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) (50), the Violence Risk Appraisal Guide (VRAG) (52), and the HCR-20 (53). 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 regarding 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.

4. Competency

The degree of mental capacity required for competency varies according to the particular ability in question. People who are totally unable to care for themselves 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. Because adults are presumed by law to be competent, the burden of proof is on those who those 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.

People who are so impaired that they are unable to take proper care of themselves 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, caused by mental illness, may cause a person to be: 1) a spendthrift, 2) unwilling to spend money, even for necessities, or 3) unable to protect themselves from those who might attempt to secure their 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 they are making a will and that they know, without prompting, their natural heirs and the nature and extent of their property. Entering into a contract requires a greater degree of competency 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 caused by mental disease, not simply a lack of sophistication or technical knowledge.

Competency to marry requires that each partner understands that 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 (54). To evaluate the defendant's factual understanding of the 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 the defendant's 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 of whether the defendant had a factual understanding of the role of the judge and jury.

The examiner also evaluates the defendant's ability to assist their 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 secondary to paranoid delusions that the defense attorney is poisoning the defendant is evidence that the psychosis renders the defendant unable to rationally assist their attorney. In contrast, a defendant who refuses to speak to their attorney solely because the defendant prefers staying in a forensic hospital rather than face potential prison is an unwilling defendant rather than one unable to assist counsel.

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, they may be found not guilty by reason of insanity. However, the mere fact that psychosis or some other type of mental health symptom was present when the crime was committed does not ensure 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 the act, or that it was wrong (55). This is the most common test of insanity and is used in 38 states (56). This test, sometimes referred to as the "right or wrong test" has been criticized because it is limited to the defendant's awareness of their acts as compared with the defendant's ability to control their behavior because of mental illness.

The irresistible impulse test relieves a person of criminal accountability if mental disease made them incapable of refraining from the criminal act. Some jurisdictions require proof that the defendant would have committed the act even if a policeman had been standing at their elbow. The inability to control the impulse must be caused by 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" (57). At one point, the ALI test was used in 10 of 11 Federal Circuits. However, after 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 because this was perceived as making it easier to be found insane. In 1984, congress passed the Federal Rule for insanity 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" (58). The Federal version is now very similar to the original McNaughten test, which is also the test used in some variation by approximately 38 states (56).

Each jurisdiction, either through statute or case law, provides 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 caused by 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 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 the defendant 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 whether their actions were morally wrong may also be considered in determining sanity. 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, although they hide their actions from the police, whom they believe are evil co-conspirators.

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 caused by 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 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" (59).

Malpractice suits against psychiatrists and other mental health professionals have increased steadily since 1975, when only 1 in 45 psychiatrists were sued annually. By 1995, the odds of a psychiatrist being sued in any one year had increased to nearly 1 in 12, and, in some states, to 1 in 6 (60).

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. The possibility of a patient committing suicide represents one of the greatest emotional and legal concerns of clinicians. This concern is real in view of the fact that 10 to 15% of patients with major psychiatric disorders will die by suicide (61). Lawsuits involving suicide usually involve one of three scenarios: 1) an inpatient suicide in which 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 (62).

Suicidality is the most common reason for inpatient psychiatric hospitalization (63). When a patient is admitted to the hospital because of 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 (64). 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 (65).

7. The Psychiatrist as Expert Witness

Medical reports or testimony are required in more than 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 on as *expert*, rather than *fact*, witnesses. "Expert witnesses" are persons who possess facts directly related to some science or profession that 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 their direct observations, such as the information learned during an examination.

It is a fallacy to consider the psychiatric expert witness impartial. Once psychiatrists have formed an opinion, it is only human for them to identify themselves with that opinion, and hope for the success of the side that supports their 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 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 very formal and ritualized. *Direct* examination will begin with the elicitation of the psychiatrist's qualifications. The psychiatrist will then be asked to describe their examination of the patient. The psychiatrist will be asked whether they have formed an opinion with reasonable medical certainty regarding the critical 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 they have either not completed their 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 on the evaluee's statements.

The clinical examination is highly vulnerable to attack. Substantial evidence of the fallibility of psychiatric conclusions has been compiled, e.g., inter-examiner reliability of psychiatric diagnosis is only 60% (66).

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 them 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. Don't 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 on the outcome of the case.
11. Don't ever talk down to the jury. If they feel patronized, they will not accept what you are saying.
12. Don't use psychiatric jargon. It is likely to be misunderstood or made to look ridiculous.
13. Don't appear arrogant. Nothing alienates a jury more quickly.
14. Don't attempt to be humorous. A trial is a serious matter.
15. Don't 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 the cross-examiner is just doing their job.
16. Don't lose your temper.
17. Don't answer any question you don't fully understand. Ask the attorney to rephrase the question or define the terms.
18. Don't guess at an answer. It is better to say you don't know or don't remember.
19. Don't ever refuse to admit the obvious. It makes the psychiatrist look either foolish or biased.
20. Don't let a zealous attorney push you into an opinion that is not your own.
21. Don't try to avoid answering questions regarding your fee or pretrial conferences.
22. Don't 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 their own state.

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 conducting assessment and treatment recommendations based 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 to continuously practice within the standard of care expected, and respecting the dignity and autonomy of those patients we serve.

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Sleep Disorders

Thomas D. Hurwitz, MD and Carlos H. Schenck, MD

Abstract Disturbances of sleep are commonly seen in many of the DSM-IV Axis I 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 sleepwalking/sleep terrors and rapid eye movement (REM) sleep behavior disorder. In each case, diagnostic criteria are described, based both on the American Psychiatric Association *Diagnostic and Statistical Manual*, 4th edition, text revision (DSM-IV-TR) and the *International Classification of Sleep Disorders*, 2nd 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 Hypersomnia · Insomnia · Narcolepsy · Obstructive sleep apnea · Parasomnias · REM-sleep behavior disorder · Restless legs syndrome · Sleep · Sleepwalking

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.

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*, 4th edition, text revision (DSM-IV-TR) (1), reveals the presence of sleep symptoms as diagnostic criteria in major depressive episode and disorder, manic and hypomanic episodes, bipolar disorders, dysthymic disorder, cyclothymic 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 seems to be predictive of subsequent development or relapse of alcohol dependence and depression. Persisting short time latencies between sleep onset and the first rapid eye movement (REM) period, as well as diminished low frequency sleep–electroencephalogram (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 (CBT). 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 seems 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 previous nocturnal sleep (8, 9). In view of its effects on human consciousness, sleep is clearly "of the brain, by the brain, and for the brain" (10).

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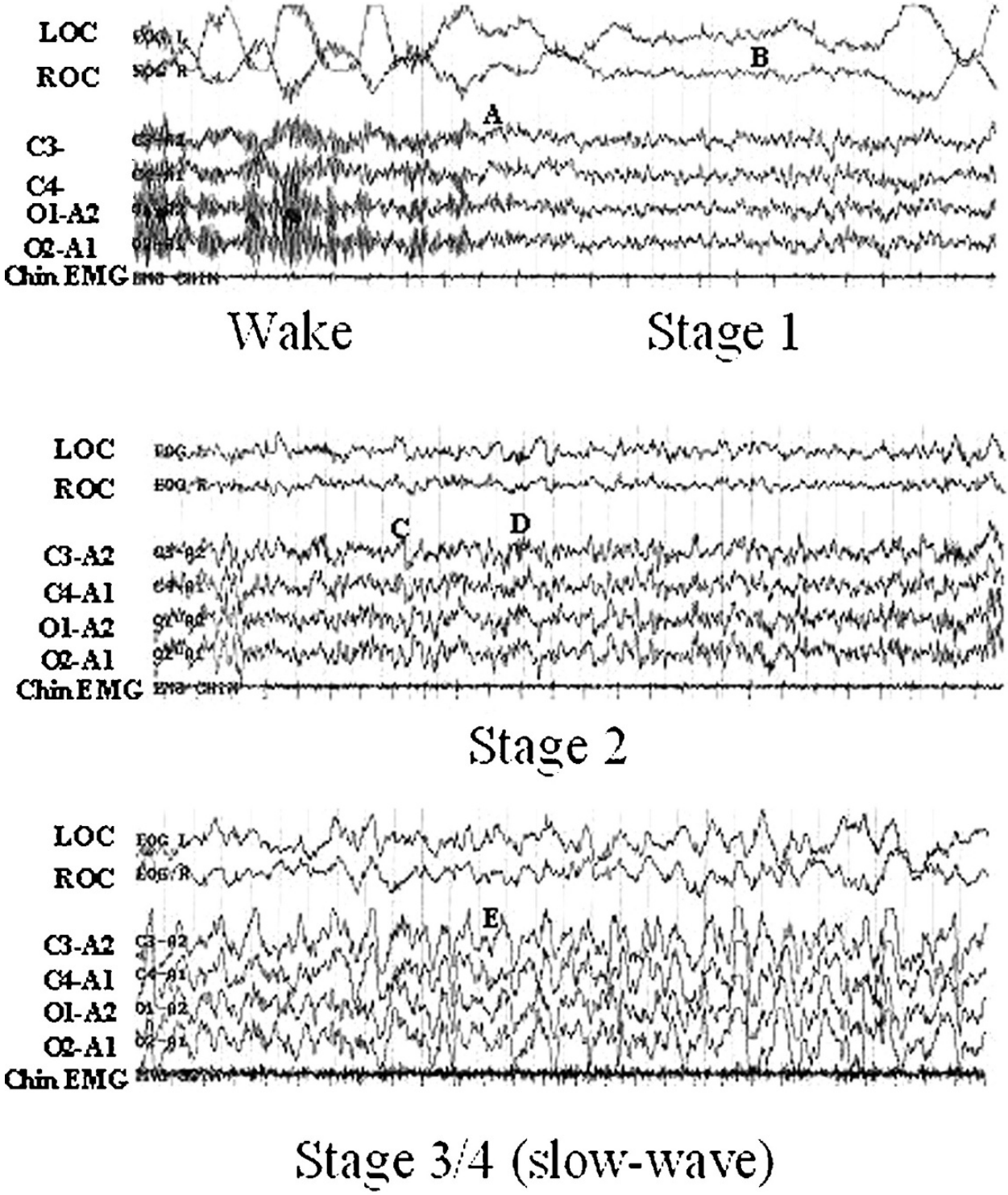

FIGURE 37.1. Polysomnographic patterns characteristic of wakefulness and sleep. Note the disappearance of the wakeful alpha rhythm with slower, relatively low-voltage EEG activity (*A*) and the appearance of slow, rolling eye movements (*B*) indicative of the transition from wakefulness to stage 1 sleep. Subsequently, the presence of biphasic K-complexes (*C*) and 12- to 14-Hz bursts of spindle activity (*D*) are associated with stage 2 sleep. This is followed by higher voltage, slow (2-Hz) EEG waves (*E*) characteristic of stages 3/4 or "slow wave sleep."

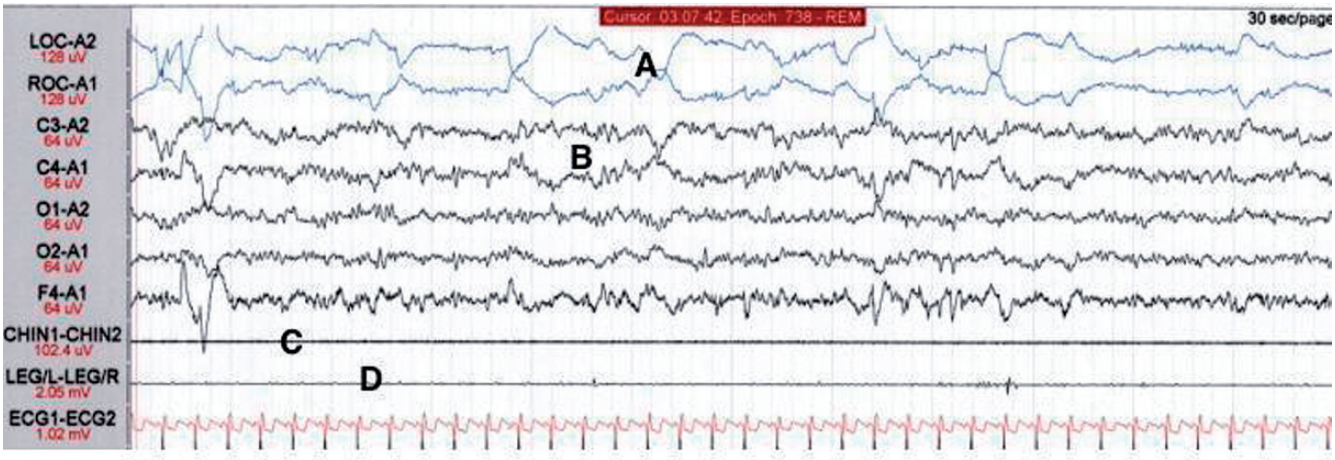

FIGURE 37.2. A 30-second epoch of REM sleep is exemplified by rapid eye movements (*A*), desynchronized low voltage mixed frequency EEG with occasional saw-tooth wave forms (*B*), absent muscle tone in the chin EMG (*C*), and no movement of lower extremities (*D*) (*see* Color Plate 9, following p. 650).

Physiological manifestations of sleep are measured clinically by polysomnography (PSG), with monitoring of brain electrical activity (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 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). 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 1 of non-REM sleep. Soon thereafter, the EEG includes intermittent bursts of 12 to 14 Hz activity, known as sleep spindles, representing thalamocortical 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 2 sleep, which progresses variably to a pattern of slower, 2-Hz EEG activity that designates stage 3 ($\geq$20% of the 30-second epoch) and stage 4 ($\geq$50% of the epoch). These two stages are generally combined and referred to as slow-wave sleep. A revised scoring manual now designates stages of non-REM sleep as N1, N2, and N3 (378). 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 approximately 90 minutes of non-REM sleep, there is typically a period of marked reduction of peripheral muscle tone on EMG, with 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 cardiorespiratory rhythms, and vivid dreaming. After a variable period of minutes, there is resumption of non-REM sleep before the next periods of REM, which recur with a periodicity of approximately 90 minutes. Each successive REM period is longer in duration with a tendency for more frequent eye movements (Figs. 37.1 and 37.2 and Color Plate 9, following p. 650).

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, whereas lesions of the anterior hypothalamus caused prolonged insomnia (12). By mid-century, Moruzzi and Magoun described the reticular activating system from the rostral pons through the midbrain reticular system (13). 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 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 multisource 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, which 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 previous 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 previous wakefulness. The second important regulatory influence is the circadian system (process C) 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. All is well when the homeostatic drive is maximal while the circadian wake signal decreases, and both processes are synchronized to the desired bedtime (14) (Figs. 37.3 and Color Plate 10, following p. 650).

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 such as cataplexy, visual imagery, and sleep paralysis; and parasomnias such as 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 (OSA), 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.

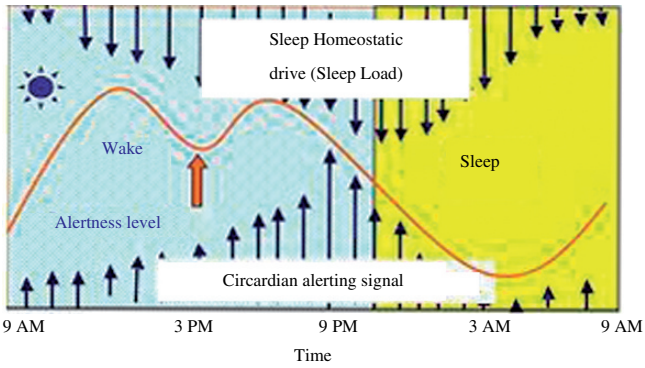

FIGURE 37.3. The two-process model of sleep–wake regulation. With ongoing wakefulness, the homeostatic sleep drive (process S) increases, reaching its maximum level as the circadian alerting signal (process C) diminishes. With ongoing sleep, the homeostatic drive dissipates, and wakefulness ensues as the circadian signal intensifies in the morning. Reprinted with permission from Elsevier, Inc (*see* Color Plate 10, following p. 650).

3. Insomnia

3.1. Definition

Insomnia has traditionally been regarded as a symptom of difficulty with sleep onset or maintenance. The DSM-IV-TR includes primary insomnia as an Axis I disorder, characterized by difficulty initiating or maintaining sleep, or nonrestorative sleep lasting at least 1 month. It must be associated with clinically significant distress or impairment in social, occupational, or other types of functioning and not be associated exclusively with another sleep disorder. It cannot be associated exclusively with a psychiatric disorder or be the direct effect of a substance or a general medical condition (1).

The ICSD-2 defines general criteria for insomnia as 1) a complaint of difficulty initiating sleep, difficulty maintaining sleep, waking up too early, or sleep that is chronically nonrestorative or poor in quality; 2) this occurs when there is otherwise adequate opportunity and circumstances for sleep; and 3) 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 caused by mental or medical disorders, inadequate sleep hygiene, and insomnia caused by drug or substance use (15).

Closest to the primary insomnia of DSM-IV-TR are psychophysiological insomnia and idiopathic insomnia. The latter is distinguished by: 1) onset during infancy or childhood, 2) no identifiable precipitant or cause, and 3) 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 one of 1) excessive focus on and elevated anxiety about sleep, 2) 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, 3) better sleep in novel situations away from home, 4) mental arousal in bed with intrusive thoughts or the perception of inability to stop thinking that prevents sleep, and/or 5) 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 (15).

3.2. Epidemiology

The median prevalence of insomnia seems to be 35% in the general population with 10 to 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 (16). If daytime consequences are included with insomnia symptoms, the prevalence ranges between 9 and 15%. Dissatisfaction with sleep quality or quantity is reported by 8 to 18% of people and actual insomnia diagnoses probably occur in approximately 6% of the population, remaining stable across age groups, in contrast to the increase of insomnia symptoms (17). Despite the prevalence of insomnia, the majority of sufferers do not seem to discuss it with their primary care physicians (18–20). In the elderly population, serious insomnia may affect at least 20 to 40% of people (21–24).

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 regarding 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 (25). 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. Despite these symptoms, patients do not fall asleep during the day, reflecting a generally hyperaroused state (26–28).

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 (16, 23, 29–35).

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. Although 10 mg zolpidem 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 during the next 4 weeks.

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 (OSA), parasomnias, or movement disorders are suspected (36). Quantitative electroencephalography has shown increased beta (fast frequency) activity and decreased theta and delta (slower frequencies) during sleep, suggesting increased cortical arousal (37, 38). 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 insomniac patients, but still more than healthy sleepers (39). 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 (Fig.37.4) (40). 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 healthy control subjects (41).

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 a 1-month duration (42–44). 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 (45). Hence, there is a conditioned pattern

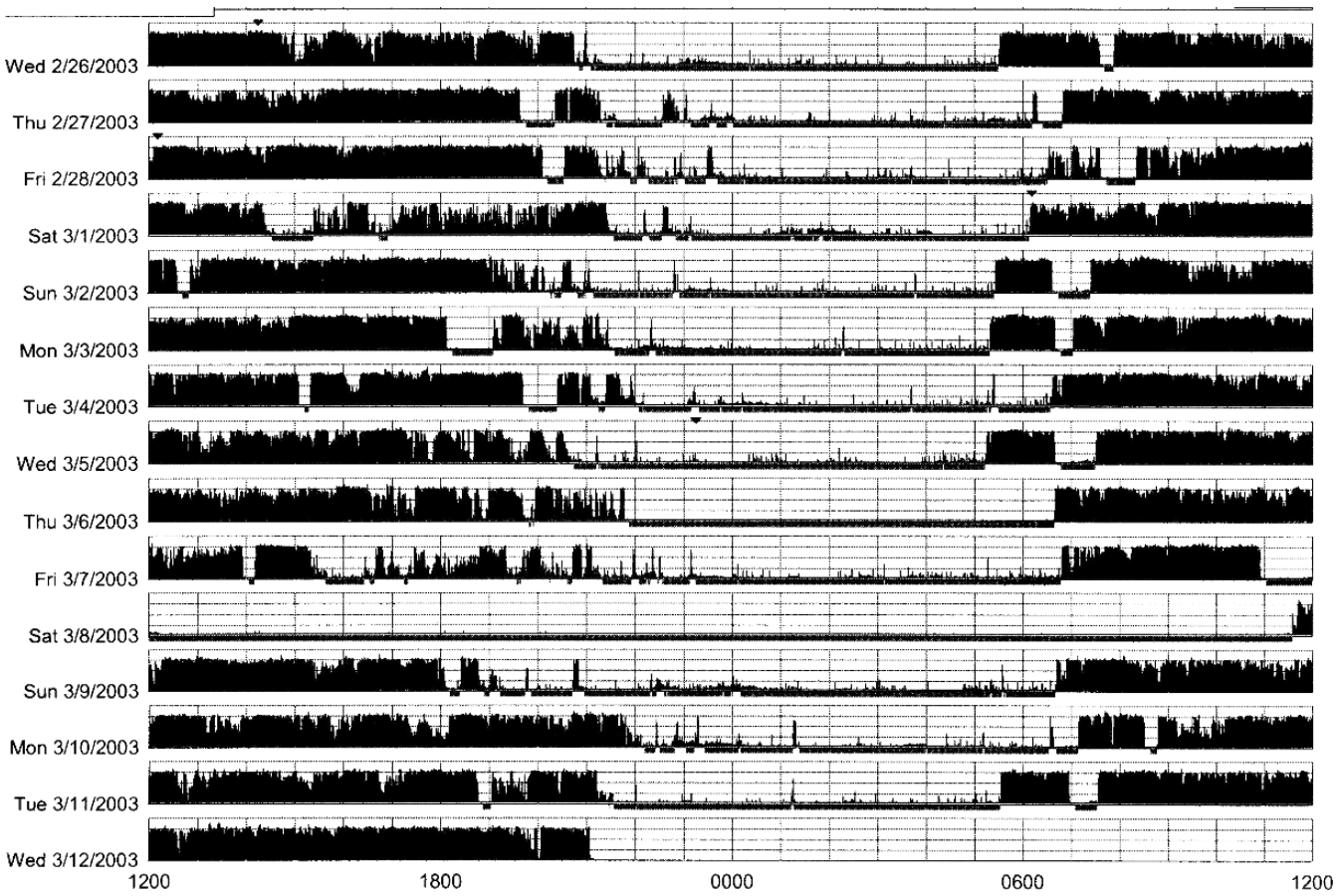

FIGURE 37.4. A wrist-worn activity monitor records movements in 1-minute time bins to display a representation of rest–activity (sleep–wake) cycling during a 2-week period. Note that during the period with absolutely no detectable movement, the device was not being worn. When coupled with a subjective sleep–wake diary, actigraphy can provide information from many successive days and nights.

of hyperarousal that develops in the situation in which sleep is sought and desired. Some individuals report disturbed sleep onset and maintenance since early childhood, which constitutes idiopathic (childhood-onset) insomnia (46).

3.7. Differential Diagnosis

As described above, most insomnia is temporally related to precipitating factors. When it does not seem 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 despite 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 (42).

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, although 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 (47).

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 years and the predominant complaint is sleep onset difficulty (48). Abnormal elevations of urinary free cortisol levels reflecting elevated arousal are consistent with a sleep disturbance related to abnormal catecholamine metabolism (49). Not only is insomnia a ubiquitous symptom of depression, but also it seems from a few longitudinal studies that it is predictive of future incidence of depression (50–52). 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 (53, 54).

Up to 40% of adults with insomnia in the general population (50) and approximately 75% of patients with insomnia in sleep center or primary care clinics have a psychiatric disorder (55). Approximately 71% of these will have dementia, 69% depressive disorders, 61% anxiety disorders, and 32% alcohol dependence (56). Polysomnographic studies of depression have shown diminished slow-wave sleep (stages 3 and 4), frequent nocturnal arousals and awakenings, as well as reduced time between sleep onset and the first REM period (57, 58). By PET imaging, there seems to be less cortical and thalamic deactivation in depressed patients compared with healthy control subjects 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 (59).

3.9. Treatment

Treatment of comorbid or secondary insomnia is directed at the underlying disorder. The sleep symptom may influence the choice of such therapy, such as a sleep-supporting antidepressant, analgesic, neuroleptic, antacid, etc. If insomnia persists despite initial therapy, an adjunctive hypnotic drug may be indicated. If insomnia persists with resolution of apparent secondary or comorbid disorders, then treatment as for primary insomnia should be initiated. Two basic treatment approaches are commonly used, cognitive–behavioral therapies and pharmacotherapy.

3.9.1. Nonpharmacological 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 to 10 sessions. A traditional element is stimulus control therapy, which acknowledges the bedroom as a conditioned stimulus for wakefulness where insomniac patients 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 (60, 61). Another component, sleep restriction therapy, calls for reducing the time spent in bed to diminish wakefulness during that period and increase the homeostatic sleep drive, which derives from partial sleep deprivation (62). Relaxation training can be added to decrease arousal (63). 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 (64, 65). CBT is clearly effective for reduction of sleep onset latency and subsequent awakenings in at least 50% of patients (63, 66–68). Benefits seem 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 (63, 69–71). 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.

3.9.2. Pharmacological Therapy

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), BZ receptor agonists (BZRA), and the new 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. The BZs currently approved in the United States for treatment of insomnia include flurazepam, triazolam, quazepam, estazolam, and temazepam. BZRAs include zolpidem, zaleplon, and eszopiclone. These drugs are all rapidly absorbed and variably metabolized and excreted. Two BZs, flurazepam and quazepam, have long durations of action with elimination half lives ($t_{1/2}$) of 48 to 120 hours. The BZRAs include an ultrashort duration drug, zaleplon, with a $t_{1/2}$ of 1.0 hour. All of the others are of intermediate (temazepam, estazolam, eszopiclone with a $t_{1/2}$ of 5–15 hours), and short duration (triazolam and zolpidem with a $t_{1/2}$ of 1.5–5 hours). As a rule, the longer-duration BZs 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 healthy sleepers, BZs tend to decrease sleep onset latency, wake after sleep onset, stage 1 sleep, stage 3/4 sleep, and REM. They tend to increase total sleep time, sleep efficiency, stage 2 sleep, EEG fast activity, and latency to the first REM period. When studied exclusively in insomniac patients, predominant effects are increased total sleep time and reduced stage 3/4 sleep. Zolpidem has very little effect on the structure of PSG measured sleep other than shortening latency and increasing continuity (72). In a PSG study of insomnia treated with zolpidem, drug treatment lowered sleep latencies to persistent sleep from 61.9 ± 6.7 minutes to 23.7 ± 2.3 minutes (73).

Most studies of these agents have been conducted during short periods, typically up to 8 weeks, with the exception of intermittent dosing of zolpidem during 12 weeks, and nightly eszopiclone during a 6-month extension. These studies 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, although there are no studies yet providing citable evidence (43, 74–76).

Many side effects are related to elimination half-life. Withdrawal effects including rebound insomnia (i.e., worse than pretreatment) are typically not seen with long-duration drugs and increase with decreasing half-life BZs (77–79). This is a transitory one- to three-night phenomenon when it occurs. It is not appreciably associated with BZRAs. Anterograde amnesia can be problematic and typically associated with the shorter-duration BZs and BZRAs. It is likely dose-related and has been particularly noted with triazolam (80, 81). Zolpidem has been associated with unusual sleepwalking with sleep-related eating (82, 83), as have risperidone and olanzapine (84, 85). It is possible that the perception of continuous, refreshing sleep is, in part, related to the anterograde memory inhibition of BZRAs (86).

Ramelteon is a melatonin-1 and -2 receptor agonist that is available in 8 mg dosage form. It has $t_{1/2}$ of 2 to 5 hours and no evidence of rebound insomnia, tolerance, or amnesia. It has been reported to benefit primary insomnia in younger and older adults (87, 88). Animal data has documented efficacy for re-entrainment of circadian rhythm sleep disorders (89).

3.9.2.2. Other Drugs

Many other drugs have been prescribed to treat insomnia. A large study based on a nationally representative Physician Drug and Diagnosis Audit of approximately 3,400 physicians during 2002 cites "drug occurrences" in millions for trazodone (2.7 million) 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 million), the second ranking drug, followed by amitriptyline (0.8 million), mirtazapine (0.7 million), quetiapine (0.5 million), olanzapine (0.2 million), hydroxyzine (0.3 million), doxepin (0.2 million), cyclobenzaprine (0.2 million), and diphenhydramine (0.2 million). Only 4 of the top 16 drugs were US Food and Drug Administration (FDA) approved for insomnia, not including clonazepam (0.4 million), alprazolam (0.3 million), and lorazepam (0.3 million), which are not so-approved, but which also appeared. Despite 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 (90, 91).

Trazodone, a weak selective serotonin reuptake inhibitor (SSRI), also inhibits 5-HT-1A, -1C, and -2 receptors. It is a moderate inhibitor of histamine-H1 receptors, but is not anticholinergic (92). Although trazodone may increase stages 3/4 sleep, it has little effect on REM. Although it may diminish sleep onset latency, increase total sleep time, and increase sleep efficiency in some studies of healthy control subjects or depressed patients, these effects were limited to a single week for insomnia patients (93–97).

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 (98–100). A striking finding in patients treated with SSRIs is persistence of slow eye movements well into consolidated non-REM sleep. This is of unknown clinical significance, although it indicates an enduring neurophysiological response from previous exposure to SSRI drug. This can continue even long after the drug has been discontinued (101).

The tertiary amine tricyclic antidepressants (TCAs), doxepin and amitriptyline, inhibit histamine, acetylcholine, and alpha-1, and alpha-2 adrenergic receptors. Antihistaminic activity mediates sedation, whereas anticholinergic activity contributes to the inhibition of REM sleep seen with these drugs (102). Trimipramine does not seem to affect REM sleep. TCAs do have documented capacity to reduce sleep latency and improve sleep efficiency in healthy control subjects and depressive patients, but only limited data show improved sleep efficiency for primary insomnia (103–107).

In a large study of major depressive patients 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 (100).

Mirtazapine is a potent antihistamine that also antagonizes 5HT-2, and alpha-1 and alpha-2 noradrenergic receptors. It seems to decrease sleep latency and increase stage 3/4 sleep in healthy adults, although not as clearly in depressed patients. Its sleep-favoring effects seem to be more potent at low doses, where antihistaminic effects may predominate (108–110).

Other antihistamines, such as diphenhydramine, that can act centrally to mediate sedation do not seem to be potent inducers of polysomnographic sleep. There also seems to be rapid tolerance to this effect. Coupled with anticholinergic, cognitive, psychomotor, and anorectic side effects, diphenhydramine is a less ideal hypnotic, despite its 16th place frequency of use in 2002 (90, 97, 111–114).

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. No studies, however, address the use of these drugs for insomnia.

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 12 patients, compared with 409 ± 40 minutes in the 10-patient 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 (115). Also in schizophrenic subjects, clozapine was associated with improved sleep continuity and increased stage 2 sleep, but no significant change of sleep latency from the beginning of therapy through at least 7 weeks of treatment (116). 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 (117).

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 (118).

Olanzapine, another potent 5HT-2A and -2C antagonist, also has affinity for muscarinic cholinergic, alpha-1 adreno-, and histamine H1 receptors. It is thought 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 (119, 120).

Risperidone, also a 5HT-2 blocker, has been shown to decrease REM sleep duration in healthy control subjects and treatment-resistant depressed patients in whom total and stage 2 sleep increased. It did not affect REM latency (121).

4. Movement Disorder: Restless Legs Syndrome

4.1. Definition

Although categorized as a sensorimotor or movement disorder, restless legs syndrome (RLS) is a frequent cause of difficulty falling asleep. Originally described by Ekbom (122), it remains an interesting and challenging clinical problem. Diagnostic features have been elucidated by an international RLS study group and the ICSD-2 diagnostic criteria for adults include: 1) urges to move the legs, usually because of or associated with discomforting sensations in the legs; 2) the urges or sensations begin or worsen with rest or inactivity; 3) they are partially or completely relieved during movement of the limbs; 4) they are predominantly or exclusively present during the evening or night hours; and 5) the symptoms are not related to any other sleep, medical, neurological, psychiatric disorder, or to medication or substance use disorders (15).

4.2. Epidemiology

RLS seems to be increasingly common, with a prevalence estimated to be 10 to 15% of the general population, and is more frequently found in women than men (123–127). It is found in 20% of pregnant women (128, 129), 20 to 62% of patients with chronic renal failure treated with dialysis (130, 131), and 5.2% of patients with polyneuropathy (132).

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, although 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 (133, 134).

4.4. Case History

A 33-year-old woman complains of difficulty falling asleep for many years. This worsened during each of her two 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 will get up and walk in circles around her living room before returning to bed. She falls asleep after 60 to 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 approximately 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. Her hemoglobin level is 14.1 mg/dl and serum ferritin is 87 μg/L. After beginning 0.125 mg pramipexole taken 2 hours before bedtime and increasing to 0.375 mg, she reports improvement of sleep onset and daytime symptoms.

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 μg/L can be associated with increasing severity of RLS (134–138). Polysomnographic studies of sleep in patients with RLS demonstrate periodic leg movements during sleep (variably associated with EEG arousals) and initial wakefulness in 80 to 90% of cases (139). 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 RLS (140). Actigraphic monitoring of periodic leg movements has also been used (141).

4.6. Clinical Course

RLS may occur at all ages and can be misdiagnosed as "growing pains" in children (142, 143). When beginning before age 45 years, symptoms progress slowly from an intermittent to a more frequent pattern and may become daily by 40 to 65 years of age. Late onset RLS 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, theater, or work setting (123, 144).

4.7. Differential Diagnosis

Traditional neuroleptic medications antagonizing dopamine receptors may induce akathisia resembling RLS, 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. Although some RLS is experienced as painful, movement as a response to pain from various sources is not typically based on an urge to move per se (15). Insomnia with anxiety and psychomotor agitation is likewise not associated with an urge to move or relieved by it.

4.8. Etiology

There is a genetic predisposition with a familial distribution of RLS, which occurs three to six 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 (15, 139). The pathological basis of RLS 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 (145). A genetic variant on chromosome 6p21.2 has been found to be associated with susceptibility to RLS with periodic limb movements during sleep and inversely associated with iron stores (379). As noted above, RLS occurs frequently in patients with iron deficiency, severe renal disease, and pregnancy. Peripheral neuropathy is often associated with RLS, and its associated pain may contribute to the urge to move. When measured, cerebrospinal fluid (CSF) ferritin levels have been 65% lower than normal peripheral levels in patients with RLS, suggesting specific brain iron deficiency (146). A decreased density of dopamine D-2 receptors has been observed in the striatum of RLS patients by PET and single-photon emission computed tomography (SPECT) imaging (147–149). Many sedating antihistamines, numerous antidepressant drugs (other than bupropion with its dopaminergic property), and dopamine antagonists will precipitate or worsen RLS (15, 150).

4.9. Treatment

A treatment algorithm has been proposed, based on the frequency of RLS symptoms (134). For mild, intermittent RLS, nonpharmacological 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 levels are less than 20 μg/ml and considered if ferritin is less than 50, which has been associated with worsening of RLS (135, 137). The initial pharmacological strategy for intermittent symptoms is typically prescription of a dopaminergic agent. The initial choice could be 25 mg carbidopa plus 100 mg levodopa, as needed, but alternatives include dopamine agonists, 0.125 mg pramipexole or 0.5 mg ropinirole, taken 2 hours before bedtime, as needed, and titrated further as indicated (151–154). 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 RLS. Other options include the low-potency opioids, propoxyphene or codeine; the opioid agonist, tramadol; the BZs, temazepam or triazolam; or the BZRAs, zolpidem or zaleplon, which may be considered as needed.

For RLS occurring nightly, regularly administered therapy is needed and includes the same nonpharmacological techniques as well as a nightly dopamine agonist, gabapentin, or low-potency opioids. Refractory RLS may develop with inadequate or decreasing benefit from dopamine agonists, intolerable side effects, and/or augmentation of RLS symptoms, causing occurrence earlier in the day. 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. An important side effect of dopamine agonist therapy is the emergence of impulse control disorders, such as compulsive gambling, buying, and sexual behavior, which has been reported in patients with Parkinson's disease on these drugs. All patients treated with dopamine agonists must be warned about this risk, which can occur in as many as 4 to 8% of patients (155–157). Change to a high-potency opioid or tramadol may be needed (134). In severe cases of RLS, both associated with prominent leg pain or not, methadone therapy on a long-term basis may be required as a monotherapy or combined with a dopaminergic agent (158).

5. Obstructive Sleep Apnea

5.1. Definition

Among the breathing-related sleep disorders in the DSM-IV-TR 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). Although not formally defined in the DSM-IV-TR, it is designated as a condition resulting in excessive sleepiness or insomnia, and not accounted for by another mental disorder, substance, or medical condition (1).

The ICSD-2 defines OSA as marked by at least 1) complaints of unintentional sleep episodes during wakefulness, daytime sleepiness, unrefreshing sleep, fatigue, or insomnia, OR 2) wakenings 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, AND 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, or respiratory effort-related arousals (RERAs), if EEG arousals are 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 15 or more of these scoreable events per hour of sleep (15).

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 additional extraluminal pressure there is to collapse the airway. Craniofacial abnormalities such as small mandible, macroglossia, retrognathia, and acromegaly also predispose to OSA (159). 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 (160). Obesity is common and a linear correlation has been established for neck girth and severity of OSA (161, 162).

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 airflow limitation and increased inspiratory effort that can lead to RERAs. These may be inferred from a pattern of crescendo snoring on successive preceding breaths, characteristic flattening pattern on a nasal pressure monitor of airflow during sleep, or from increased intrathoracic pressure on esophageal manometry, which is not frequently used 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 after 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 to 15 events/hour would generally be considered as mild, 15 to 30 events/hour, moderate, and at least 30 events/hour, severe OSA. When these events occur with clinical symptoms, the condition is designated as obstructive sleep apnea syndrome (OSAS).

5.3. Clinical Picture

The clinical presentation of OSAS includes reports of snoring, often with apneas witnessed by bed partners, and excessive daytime sleepiness (163). 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, although 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 (164, 165). The degree of objectively measured sleepiness (presumably related to sleep fragmentation) varies with the AHI within individuals (166). 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 after therapy (167). Still, however, only 35% of individuals with AHI of at least 30 events/hour may report symptomatic sleepiness (166). The most dramatic negative outcome of excessive sleepiness is drowsy driving (168–170). Although 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 (171–177). A validated questionnaire has shown usefulness for diagnosing OSAS based on 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 (178).

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 nondepressed persons, even when controlled for obesity and hypertension. Approximately 20% of individuals with one of these disorders seem to have the other as well (179). 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 with healthy control subjects in that study, incidence of depression increased by factors of 2 for mild and 2.6 for moderate or worse sleep-related breathing disorder (180). In a cross-sectional study at a large Veteran's Administration medical center, patients with OSAS had statistically significantly increased prevalence of a number of psychiatric disorders when compared with patients without OSAS. Odds ratios were 2.67 for depressive disorders, 16.67 for anxiety disorders, 11.85 for PTSD, 5.13 for psychotic disorders, 4.06 for bipolar disorder, and 2.13 for dementia (181). The fatigue associated with comorbid depression may itself account for some of the symptomatology of OSAS when the two conditions overlap (182–184). This relationship is supported by the improvement of depressive symptoms with treatment of OSAS (185–187).

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 seem 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 (171, 188). Vigilance and attentional capacity deficits most resemble the effects of chronic partial sleep loss (189, 190). A large meta-analysis has shown untreated OSA to have no significant effect on 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 (191).

5.4. Epidemiology

Widely cited information regarding epidemiology of OSA comes from a number of groups, including the Wisconsin Sleep Cohort and the multicenter longitudinal Sleep Heart Health Studies that have been underway for many years. These data, generally based on internally consistent definitions and methodologies, permit the conclusion that 20% of normal-weight white adults in the United States have AHI of at least 5 events/hour and 6.7% have AHI of at least 15 events/hour. Up to 5% of adults are likely to have OSAS with respiratory obstruction, daytime sleepiness, and/or other symptoms. Prevalence among women is approximately half of this, although their risk increases with postmenopausal status. Predisposing features include obesity, advancing age, and snoring (192–195).

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, although he denies 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 (CHF), gastroesophageal reflux disorder, noninsulin-dependent diabetes, and schizophrenia. On PSG, he is found to have an AHI of 80 events/hour with an oxyhemoglobin desaturation nadir of 78%. Continuous positive airway pressure (CPAP) at 18 cm is effective, but he is unable to tolerate the mask despite extensive attempts at desensitization and numerous mask configurations. Titration with bilevel 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.

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 Fig. 37.5. Additional limited diagnostic instruments are being developed and have demonstrated usefulness for cases with high pretest probability in patients who are being evaluated for obstructive sleep apnea. These include cardiopulmonary monitors of respiration only, portable PSG, and peripheral arterial tonometry (PAT), which measures autonomic manifestations of respiratory obstructive events (196, 197, 380).

The overall total of apneas, hypopneas, and RERAs per hour describes the rate of sleep fragmentation relevant to subsequent daytime dysfunction (198). Formerly, the disruption of sleep caused exclusively by RERAs was known as upper airway resistance syndrome (UARS) and recognized as a cause of daytime sleepiness (199). It is now subsumed under the diagnosis of OSAS.

5.7. Clinical Course

OSA can begin in infancy and may be related to craniofacial anatomy and nasal airway deficiency (200). In children and adults, adenotonsillar hypertrophy can often account for the emergence of the disorder. Typically, OSA increases with age, although elderly individuals may have fewer daytime symptoms than middle-aged counterparts (201). During an 8-year follow-up study in the Wisconsin Sleep Cohort, the AHI increased in all groups, including healthy control subjects, but most prominently in those with obesity and habitual snoring subjects (195).

The association of OSA with increased mortality has been clearly documented since 1988, when patients with an apnea index greater than 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 (202).

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 (203). Hypertension is associated with OSA, in part relating to vasoconstriction responsive to elevated endothelin function and decreased levels of nitric oxide (204, 205). Oxidative stress and inflammatory processes may be proponents of the cardiovascular risk (159). There is a clear relationship between OSA and the development of hypertension

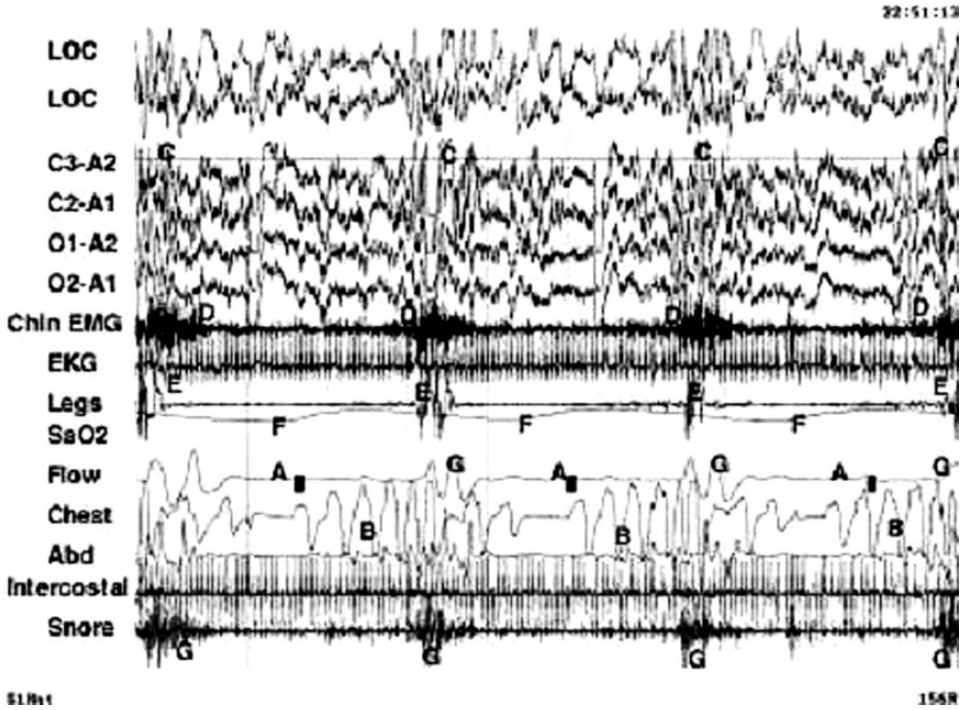

FIGURE 37.5. A 2-minute window demonstrates four obstructive apneas, with cessation of air flow (*A*) in the presence of persisting thoracic and abdominal manifestations of respiratory effort (*B*). These events are followed by EEG arousal (*C*) and bursts of chin muscle tone (*D*), leg movements (*E*), desaturations of oxyhemoglobin (*F*), and resumption of airflow with snoring (*G*).

(206). 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 (207), and these patients may report lesser degrees of daytime sleepiness than those without CHF (208). Many patients with OSA have atrial fibrillation, but it is not yet clear whether this is of etiological relevance in either direction (209). Additionally, insulin resistance, diabetes, and increased leptin levels occur more in patients with OSA than in weight-adjusted comparison subjects (210, 211).

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.

5.9. Treatment

Before the introduction of CPAP, the primary therapy for severe OSA was tracheostomy. This produces immediate benefit caused by bypass of the upper (pharyngeal) airway space, allowing unimpeded ventilation. Weight loss for overweight patients remains a strong component of therapy, although success is difficult to achieve. Hence, bariatric surgery and other means of weight loss have been used with definite improvement (195, 212). The standard treatment for OSA is CPAP, developed in the 1970s to provide a pneumatic splint for the upper airway by administration of positive pressure through a nasal or oronasal mask interface (213). Pressure is initially determined by titration during PSG, although a number of automated CPAP machines are available to adjust pressure based on machine response to airflow 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 (214, 215). Although long-term outcomes are not clearly known, CPAP in the short term has been shown to improve endothelin levels and blood pressure (205, 208, 216, 217), nitric oxide levels (218), glucose intolerance (219, 220), leptin levels and central obesity (221), left ventricular ejection fraction (208), urinary catecholamine levels (222), and the recurrence rate of atrial fibrillation (223). Unfortunately, adherence to nightly use of CPAP remains much less than desired for many reasons, including claustrophobia, interface failures, and other determinants of motivation (224). Some patients can use desensitization techniques but others may ultimately be unable to benefit from CPAP (225).

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 used. Uvulopalatopharyngoplasty alone is frequently ineffective (226). When done in combination with establishment of forward tension on the base of the tongue, efficacy can be increased. In cases of severe maxillofacial abnormality, advancement of both maxilla and mandible can be performed (227–229). Oral appliances that hold the mandible in an advanced position during the night can be effective (198). 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 after treatment of OSA have been shown to benefit from modafinil (230).

6. Hypersomnia

6.1. Definition

The DSM-IV-TR distinguishes two basic categories of disorders of excessive sleepiness, primary hypersomnia, and narcolepsy. The former is described as 1) excessive sleepiness for at least 1 month (or less if recurrent) with either prolonged sleep episodes or daytime sleep episodes almost daily, 2) causing clinically significant distress or impairment in social, occupational, or other areas of functioning. It is 3) not caused by insomnia, any other sleep disorder, insufficient amount of sleep, 4) any psychiatric disorder, or 5) any substance or general medical condition. The recurrent form includes periods of sleepiness lasting at least 3 days several times annually for at least 2 years. Narcolepsy is defined as 1) irresistible attacks of refreshing sleep occurring daily over at least 3 months with 2) one or both of cataplexy (spells of diminished muscle tone) and/or recurrent intrusions of presumed REM sleep components into the transition between sleep and wakefulness. These are hypnagogic (at sleep onset) or hypnopompic (at sleep offset) hallucinations or sleep paralysis at the beginning or end of sleep episodes. The disturbance is 3) not caused by a substance or general medical condition (1).

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-IV corresponds most directly with the category known for many years as idiopathic hypersomnia. The variant of this, which was previously designated as the polysymptomatic form, is now known as idiopathic hypersomnia with long sleep time. It is defined as 1) a complaint of excessive daytime sleepiness occurring almost daily for at least 3 months. History, sleep logs, or actigraphy reveal 2) prolonged (longer than 10 hours) nocturnal sleep time and difficulty awakening fully from any diurnal or nocturnal sleep, and 3) no alternative causes are revealed by overnight PSG, which demonstrates 4) short sleep latency and longer than 10 hours of total sleep time. If MSLT is performed, 5) it reveals mean sleep latency less than 8 minutes and fewer than two sleep onset REM periods (SOREMPS) on four or five nap opportunities. In contrast, idiopathic hypersomnia without long sleep time is defined by 1) the same complaint of excessive daytime sleepiness, 2) habitual sleep of longer than 6 but shorter than 10 hours, 3) with exclusion of other sleep disorders by PSG, which 4) demonstrates a normal overnight sleep duration longer than 6 and shorter than 10 hours. MSLT must be performed and reveals 5) mean sleep latency less than 8 minutes and fewer than two SOREMPS (15).

Narcolepsy is divided into cases with and without cataplexy. In either case, there is a complaint 1) of excessive daytime sleepiness almost daily for at least 3 months. In the former case, there is 2) a definite history of cataplexy and 3) the diagnosis is, whenever possible, confirmed with nocturnal PSG and MSLT with mean sleep latency less than 8 minutes and SOREMPS recorded on at least two naps. Alternatively, a CSF hypocretin level at most 110 pg/ml or one third of mean healthy control values is diagnostic. In narcolepsy without cataplexy, there is 1) the same complaint of daytime sleepiness, but 2) cataplexy is absent, doubtful, or atypical. 3) PSG and the same MSLT findings are required. In both cases, 4) the sleepiness cannot be better explained by another sleep, medical, neurological, or psychiatric disorder, nor any substance or medication (15).

6.2. Epidemiology

Excessive daytime sleepiness as a nonspecific 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 to 3% to less than 1% of the population (231). In a large-scale telephonic inventory, as many as 1.6% of a European and United Kingdom sample nap at least twice a day. Cataplexy seemed to be overestimated at 1.6% of the same population, because most subjects who reported it did not endorse sleepiness. Diagnosable narcolepsy seemed to have a prevalence of 0.047% (232). Two other studies of narcolepsy in Italy and Finland have described prevalence between 0.026 and 0.04% (232). In Israel, prevalence as low as 1:500,000 to 1:660,000 has been reported (233), whereas, in Japan, it has been as high as 0.16% (234). 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) (235). Prevalence of idiopathic hypersomnia seems to be approximately 10% of the rate for narcolepsy (236).

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 on 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 (164, 165). Idiopathic hypersomnia patients never develop cataplexy or nocturnal sleep disturbance (236). Naps, unlike for narcoleptics, are unrefreshing and may be prolonged (237). For some patients, not only is arousal from sleep difficult, but also it can be accompanied by irritability, confusion, and motor discoordination that has been called "sleep drunkenness" (238).

The classic 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 (239). Cataplexy is a relatively brief period of diminished or lost motor tone typically precipitated by emotion, most frequently laughter (240). 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 (241). These core symptoms become a tetrad in later literature, with subsequent addition of sleep paralysis, or waking from sleep with persisting loss of muscle tone, and hypnagogic or hypnopompic hallucinations (242). 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 (hypnopompic hallucinations, sleep paralysis).

More recently, spells of automatic behavior (unrecalled, often nonsensical or "absent minded") have been described (237). Also mentioned are disturbed continuity of nocturnal sleep, which is less problematic in young patients, and 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 (243).

Narcoleptic symptoms can be misinterpreted as psychiatric, such as cataplectic gait disturbance diagnosed as psychogenic (244), and hypnopompic hallucinations as schizophrenic (245,246) or psychotic features of bipolar disorder (247,248).

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 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 despite 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 400 mg modafinil daily, his medication is changed to 40 mg methylphenidate daily with remarkable benefit. Cataplexy finally remits after the addition of imipramine, titrated to 25 mg twice daily.

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 scorable 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 at most 8 minutes as well as the occurrence of REM sleep (SOREMPS) during at least two naps (167).

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. The patient 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, whereas a mean sleep latency of less than 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 (248).

The use of a wrist-worn activity monitor coupled with a subjective sleep–wake diary can help evaluate the possibility of chronically insufficient sleep (249). Changes of pupillary diameter and light response have been used to assess nonspecific sleepiness, which is associated with miosis (250, 251).

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 approximately 25% of the general population. Approximately 40% of narcoleptic patients without cataplexy carry this allele (252, 253). More recently, determination of hypocretin (orexin) concentration in CSF has been helpful in distinguishing narcolepsy with cataplexy, for which an undetectable level is a highly specific finding. This specificity is limited to classic 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 (254, 255).

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 (236). Spontaneous remission is unlikely. The onset of narcoleptic symptoms typically occurs around the time of puberty, with peak incidence rate in the second decade (235). Many fewer cases develop in the 4th and 5th decades. The correct diagnosis is frequently delayed by up to 10 years (256). 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 they occur frequently in healthy control subjects (243). As time passes, symptoms of sleepiness can have significant negative effects on mood and health-related quality of life (257, 258). With aging, there is an increasing tendency to have more fragmented nocturnal sleep and some patients have developed REM sleep behavior disorder (RBD), also based on dysregulated REM sleep physiology (259, 260).

6.7. Differential Diagnosis

Recurrent hypersomnia, especially the Kleine–Levin syndrome, is rare (∼200 cases reported), more common in male individuals, with adolescent onset, and typically remitting after a few years. These 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 (15, 261). Hypersomnia conditions must be distinguished from behaviorally induced insufficient sleep syndrome and sleepiness caused by substances, medications, and medical disorders.

Although mood disorders are often associated with fatigue, lethargy, and/or psychomotor retardation, they are not typically associated with actual hypersomnia unless mediated by medication (262). If hypersomnia is difficult to distinguish from fatigue with depression, PSG and MSLT documentation are required (263). Other sleep disorders, such as OSA and RLS with periodic limb movement disorder, may be associated with hypersomnia. This is important, because shift work (for men), sleep restriction, antidepressant use, and possibly OSA can also be associated with SOREMPS not necessarily caused by narcolepsy (264–266). 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 (267). Secondary narcolepsy is not associated with HLA-DQB1*0602 at rates beyond those of the general population (241).

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 (268).

6.8. Etiology

The etiology of classic 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. The presence of HLA-DQB1-0602 in serum of these patients suggests an autoimmune neuronal destruction, although the mechanism of cell loss has not yet been determined. Family studies have documented the incidence of narcolepsy in 1 to 2% of first-degree relatives of patients, a modest increase of risk, although clearly more than in the general population. Slightly more, 4 to 5%, have isolated excessive daytime sleepiness. Monozygotic twin

discordance appears in 25 to 35% of reported twin pairs, further suggesting environmental influence (269).

The etiology of idiopathic hypersomnia is not known (236). Like narcolepsy, some cases seem to follow a viral illness, such as Guillain–Barré syndrome, hepatitis, mononucleosis, or atypical viral pneumonia (237). Some cases may have familial distribution in which HLA-Cw2 and DR11 alleles may appear (270).

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 although they do not entirely restore normal daytime alertness. MSLT latencies approach a maximum of approximately 50% of normal values with modafinil and approximately 65 to 75% with dextroamphetamine, methamphetamine, and methylphenidate (271). The traditional stimulant drugs act as dopamine reuptake inhibitors to enhance 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 (272). Modafinil, widely used in Europe before introduction into the United States, acts by an unknown mechanism on hypothalamic wake-promoting areas. Its half-life of elimination, 12 to 15 hours, allows for single-dosing schedules. It is also indicated for residual hypersomnia in patients treated for OSA (273). Sodium oxybate (gamma hydroxybutyrate [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 (274). Because it is a drug of considerable abuse potential, its use is very strictly regulated. It should be reserved for cases clearly not responsive to therapy that is more conventional. Cataplexy does not typically remit with stimulant or modafinil therapy, but responds to adjunctive REM-inhibiting drugs, such as tricyclic and SSRI antidepressants. Venlafaxine and atomoxetine have also been reportedly effective (237).

7. Parasomnias

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-IV-TR distinguishes nightmare disorder (formerly known as dream anxiety disorder), sleep terror disorder, sleepwalking disorder, and parasomnias not otherwise specified (1). Unfortunately, this limited categorization understates 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 1) ambulation during sleep, 2) persistence of sleep, altered consciousness, or impaired judgment and at least one of: (a) difficulty arousing the person, (b) confusion on awakening, (c) complete or partial amnesia, (d) routine behaviors occurring at inappropriate times, (e) inappropriate or nonsensical behaviors, or (f) dangerous or potentially dangerous behaviors. Sleep terrors are spells of 1) intense fear during sleep, usually initiated by a loud vocalization. These include 2) at least one of: (a) difficulty arousing the person, (b) confusion when awakened, (c) complete or partial amnesia, or (d) dangerous or potentially dangerous behaviors. 3) Both sleepwalking and sleep terrors are not better explained by any other sleep, medical, neurological, mental, substance use disorders, or medication use (15).

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 1) inability to move trunk and limbs when awakening from sleep or, in some cases, at sleep onset, lasting 2) 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 1) recurrent awakenings from sleep during very disturbing dream experiences that can include many diverse emotions, typically fear and anxiety, which are followed by 2) full alertness on awakening with clear recall of dream content. 3) There must also

be at least one of delayed return to sleep, and/or spell occurrences during the latter half of the habitual sleep period.

The quintessential REM sleep parasomnia is RBD. Diagnostic criteria include 1) polysomnographic finding of REM sleep without atonia, such as abnormal persistence of electromyographic muscle tone or excessive intermittent muscle twitching during REM sleep, and 2) at least one of a history of sleep-related behavior that is potentially or actually injurious or disruptive, or polysomnographic evidence of behaviors during REM sleep. There is also 3) absence of electroencephalographic epileptiform or clinical seizure activity during REM sleep (15).

7.2. Epidemiology

The prevalence of disorders of arousal has been estimated at 1 to 6.5% for sleep terrors, and 5 to 30% for sleepwalking in children and adolescents (275–277). It has been estimated that 2 to 5% of adults may experience sleepwalking (278–280). 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 years; 1.0% for ages >65 years), sleepwalking episodes in 2.0% (4.9% for ages 15–24 years, 0.5% for ages >65 years), and confusional arousals in 4.2% (8.9% for ages 15–24 years, 1.4% for ages >65 years). 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, excluding estimation of the prevalence of RBD that is found predominantly in the elderly (281).

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 (282). 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 (283, 284).

Spells of sleepwalking typically emerge during the first third of the sleep period, when non-REM sleep, particularly stages 3/4, predominate. They generally last for minutes to an hour, although 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 sleepwalking and sleep terrors associated with either fragmentary or elaborate dream imagery (285, 286).

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 very 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, despite usually calm and pleasant wakeful personalities. Behavioral features of the disorder are indistinguishable across sexes, ages, and presence or absence of neurological disorder (287). 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 (285, 286, 288).

Many interesting variations of these disorders have been reported. Overlapping non-REM and REM sleep parasomnias can co-occur in the same patient (289). Sleep-related eating disorder (SRED), 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, despite a drive to eat described as "out of control." There is no associated purging and more than 40% of patients are overweight (290–292). Other associated risk factors for SRED include RLS, periodic limb movement disorder, OSA, and zolpidem use, but it is also idiopathic in many cases. Sleep-related sexual behavior can also occur during sleep and may be confused with wakeful, inappropriate conduct (293, 294, 381).

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 (15).

7.4. Case Histories

7.4.1. Sleepwalking/Sleep Terrors

A 28-year-old man with a history of sleepwalking from ages of 5 to 10 years begins to have nocturnal spells increasingly frequently during the 5 months after beginning a new job. He is required to begin his workday approximately 2 hours

earlier than for his former employment. Approximately three or more times weekly, within 2 to 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 0.5 mg clonazepam taken 20 minutes before bedtime for 1 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.

7.4.2. REM Sleep Behavior Disorder

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 after prescription of clonazepam, initially 0.25 mg, 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.

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 (295). 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 stages 3/4. 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 despite the behavioral manifestations of a mixed state (296, 297).

Brain imaging studies are not used for clinical evaluation, although 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 with quiet slow wave sleep. There are also large areas of frontal and parietal cortex decrements of CBF when compared with healthy awake subjects. Sleepwalking seems to represent a concurrence of increased motor activation and decreased executive function during incomplete, disordered arousals from sleep (298) (Figs. 37.6 and Color Plate 11, following p. 650).

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 usually based on the interpretation of an experienced sleep specialist (Fig. 37.7). A scoring system, however, has been proposed to quantify the degree of abnormal motor activity (299, 300). 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 (Fig. 37.7).

Neuropsychological testing, although 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 (301).

7.6. Clinical Course

Commonly beginning in childhood, sleepwalking peaks between 11 and 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. In an early series of cases followed during longer than a decade, 11 (38%) of 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 (302). With time, this same cohort yielded a total of 17 (65.4%) of 26 patients developing a parkinsonian disorder or dementia without Parkinsonism (in one case) during an average of 13.3 years after

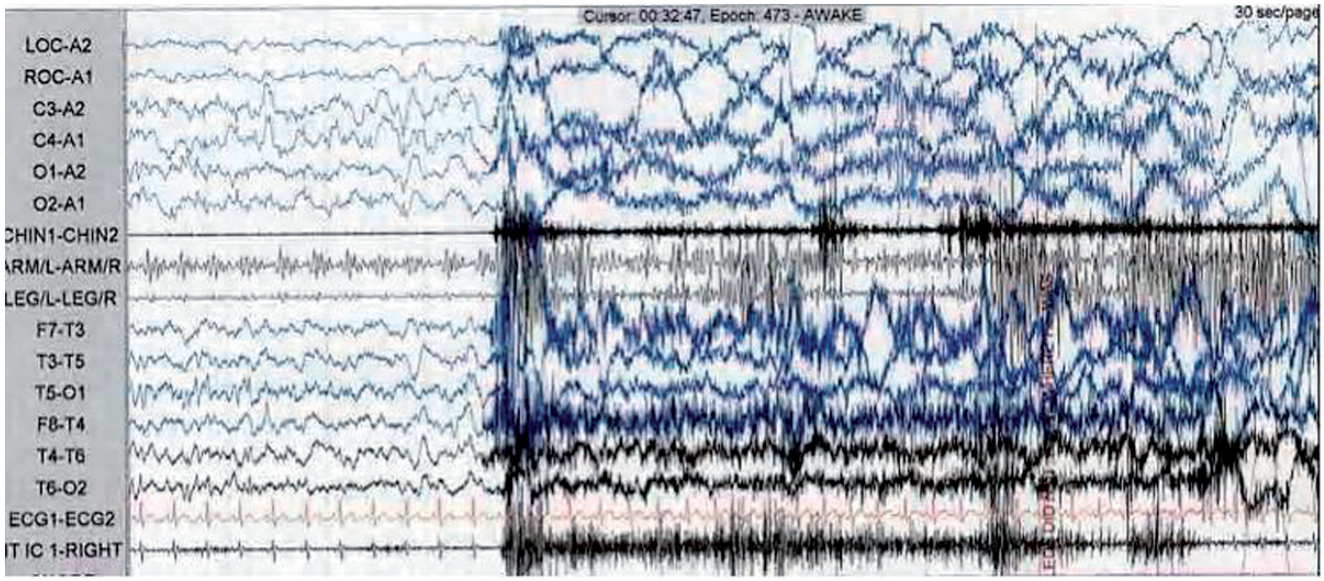

FIGURE 37.6. A 30-second epoch demonstrating an abrupt arousal from non-REM stages 3/4 sleep with subsequent movement and muscle artifact obscuring most of the underlying EEG in a patient with a history of sleepwalking. Note the absence of tachycardia, which would occur in classic sleep terrors (*see* Color Plate 11, following p. 650).

onset of RBD (303). 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 Parkinson's disease, dementia with Lewy bodies, and multiple system atrophy (MSA) (304). 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 (305).

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 (282), and, rarely, even homicide (283, 284). Spells of RBD are typically abrupt, usually of brief duration, and can yield injuries in as many as 79 to 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 (284, 306), although 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 psycho-

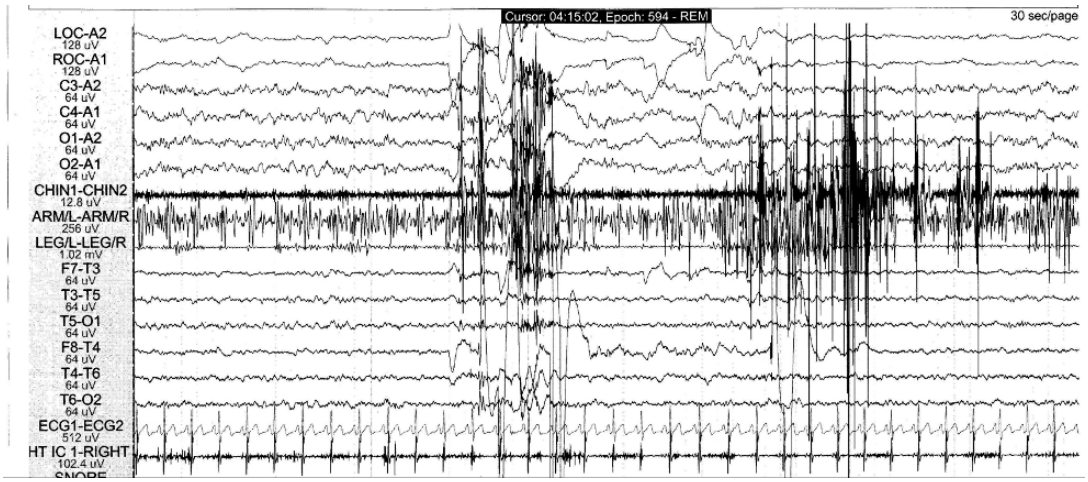

FIGURE 37.7. A 30-second epoch of REM sleep with increased tonic muscle tone in the chin EMG and bursts of phasic upper and lower extremity movement characteristic of the polysomnogram in cases of RBD.

logical stress (307, 308). 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, although no etiological relationship has been clearly established with psychiatric illness (281). 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 (309). For comparison, lifetime prevalence for major depression is 10 to 25% for women and 5 to 12% for men. Anxiety disorders have 1 to 5% lifetime prevalence (1).

7.7. Differential Diagnosis

Sleep-related seizure disorders can present as any imaginable behavioral and/or autonomic events. These have included obvious nocturnal seizures (306–316), episodic nocturnal wandering (317,318), and hypnogenic paroxysmal dystonia (a frontal lobe seizure disorder) (319, 320). Disorders of arousal and "pseudo-RBD" can be precipitated by sleep fragmentation caused by such disorders as OSA (321–325) and rhythmic movement disorders (326, 327). 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, BZ drugs that are effective in disorders of arousals and RBD may aggravate dissociative spells (328).

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 (329). Malingering remains a possibility to be kept in mind (330). 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 after 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 (15).

7.8. Etiology

The neural basis for disorders of arousal has not been elucidated, but it must reside in the dysregulation of transitions from sleep to wakefulness. Previous 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 (331). Similarly, alcohol and sedating drugs also slow this transition. Sleepwalking and sleep terrors have been associated with olanzapine (332), lithium, and other neuroleptics, often in combination (333). Sleep-related eating has been associated with zolpidem (334), olanzapine (85), and risperidone (84).

RBD 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 on experimentally induced pontine lesions in cats, has been known since 1965 (335). Most human RBD, however, is not clearly associated with such anatomical lesions. Because of the eventual development of Parkinson's 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 seems to be a herald symptom (336–338). Numerous other neurodegenerative disorders may also be associated with RBD (339). RBD can often be attributed to REM suppressing drug use as well as withdrawal, to tricyclic antidepressants; monoamine oxidase inhibitors; cholinergic drugs, such as biperiden; SSRIs; mirtazapine (reported in patients with Parkinson's disease); excessive caffeine use; and selegiline treatment of Parkinson's disease (287, 340–344). Narcolepsy, itself a disorder of physiological organization of REM sleep, has been associated with RBD (345).

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 (346–349). When there is risk of injury or serious disruption to household life, pharmacotherapy should be considered. BZs have traditionally been reported as effective, as have TCAs (350).

SRED tends not to respond to BZ monotherapy, as do sleepwalking and sleep terrors. Various combinations of levodopa, opioid, bupropion, trazodone, and BZ have been

reportedly helpful (290, 351). More recently, topiramate has become the treatment of choice (352, 353). In most published cases of automatic sexual behavior during sleep, or sexsomnia, clonazepam has been found to be very effective (293, 294, 381, 381).

More than 90% of RBD cases respond to 0.5 to 2.0 mg clonazepam at bedtime, and 12-year follow-up has indicated no significant trend toward tolerance or untoward effects, although patients must be cautioned regarding possible morning hangover sedation (354, 355). In the 10% of cases not responsive or fully remitted with clonazepam, 3 to 12 mg melatonin at bedtime has become a second-line agent and it may be considered as initial therapy for frail or cognitively impaired individuals for whom BZ is deemed contraindicated (356–358). Donepezil (359), pramipexole (360, 361), and some other drugs have been reportedly effective (287, 362). 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 RBD must have a thorough neurological assessment and they 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 before retiring to bed for the night (363, 364). Pharmacotherapy with cyproheptadine has been reportedly beneficial (365–368), although one group has reported it to be ineffective (369). Prazosin (370–375), guanfacine (376), and clonidine (377) have also been reportedly helpful.

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Neuroimaging in Psychiatry

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Abstract The tools of neuroimaging continue to improve at a rapid pace. Each technique possesses strengths and limitations. The various techniques each offer unique information. To fully understand the biological substrates of psychiatric disease, multiple neuroimaging and neurophysiological techniques must continue to develop and flourish. The goal of this chapter is to provide a solid understanding of methods frequently used in neuroimaging and neurophysiology.

Keywords Computed tomography · CT · Diffusion tensor imaging · DTI · Electroencephalography · EEG · Functional magnetic resonance imaging · fMRI · Magnetoencephalography · MEG · Magnetic resonance spectroscopy · MRS · Neurophysiology · Positron emission tomography · PET · Single-photon emission computed tomography; SPECT

1. Introduction

The tools of neuroimaging have been pivotal in literally illustrating the medical basis of psychiatry. Although not, as yet, diagnostic in themselves, these pictures depict neurobiological correlates of cognitive and affective function in psychiatric disease. In another role, the macroscopic nature of neuroimaging guides levels of inquiry that are more microscopic.

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 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 and "light up"; 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 (1). 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 (2), because it is also true that "Your data is only as good as your tools." The final principle is "follow the data." As always, it is paramount to allow the data to guide the theory, not the reverse. Just because a particular structure "should" be active in a new paradigm and another not, does not mean that real data will be that way (3).

Presently, the visualization of brain regions underlying behavior and emotion seldom impacts psychiatric care. Nevertheless, recent technical 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}F–fluorodeoxyglucose (FDG) positron emission tomography (PET) neuroimaging data of one individual 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 dementia and is being evaluated for feasibility to address other psychiatric questions, such as, "Is treatment-resistant depression a different disease than treatment-responsive depression?" Signal-to-noise ratio (SNR) in functional magnetic resonance imaging (fMRI) and electroencephalography (EEG)/magnetoencephalography (MEG) also has advanced to provide meaningful data at the level of a single subject/patient (6, 7). Perhaps future psychiatric care will entail routine neurophysiological and neuroimaging protocols.

The goal of this chapter is to elucidate: 1) the basic techniques of several major neurophysiological and neuroimaging techniques; 2) the methods applied to analyze these data; and 3) the relative strengths and weaknesses of these different techniques.

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The first section of this chapter, by PJ Pardo, describes the neurophysiological methods of intracranial electric recordings, EEG, and MEG. These technologies measure neuronal behavior directly. Sections 2, 3, and 4 provide details regarding true tomographic neuroimaging methods. The second section, by JV Pardo, details the development of computed tomography (CT) imaging. The third section, by CA Olman, explains magnetic resonance imaging (MRI) methods for structural MRI, fMRI, magnetic resonance spectroscopy (MRS), perfusion imaging, and diffusion tensor imaging (DTI). The fourth section, by JV Pardo, details the molecular imaging methods of single-photon emission computed tomography (SPECT) and PET.

Given the cognitive and affective nature of psychiatric illness, the three fields discussed each 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 key 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. These techniques certainly can be expensive, and combining them even more so. However, not having more knowledge regarding the cognitive and affective neural systems underlying psychiatric disease is costly in both human and economic terms.

1.1. Introduction to Neurophysiology

EEG and MEG offer unmatched temporal resolution (<1 ms) of brain activity. Both are passive, 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 source might be detected by E/MEG and not by either fMRI or PET. Also, brief functional connectivity (i.e., the correlation in activity between different brain regions) between sources captured by E/MEG may or may not appear in connectivity analyses of fMRI or PET data. Thus, integrating across neuroimaging and neurophysiological techniques is essential to understanding 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 involves 1) modeling the head as a conductor with one or more layers (e.g., dura, skull, scalp; each having different electrical resistance properties), and 2) determining what electric potential or magnetic field distribution would exist in the head and on the scalp based on 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. 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 for E/MEG signifies a much more difficult, and, historically, polemic issue. 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 scalp topography determined using signals from the E/MEG channels 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: use 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). Brief sources detected

by E/MEG but not fMRI/PET would disappear with this approach (modeling with fMRI/PET information produces an erroneous result; or, stated another way, fMRI/PET "in," fMRI/PET "out"). However, deep or overlapping sources with weak signal might be modeled by E/MEG with more confidence if *a priori* information is available from fMRI/PET data. How well (termed goodness-of-fit) the E/MEG modeled sources explain the topography also 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 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.

1.2. History and Data Acquisition Methods

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, et al., of 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 and arrays 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) (Fig. 38.1).

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.

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 (see Chapter 37). Present-day research studies typically use from 21 electrodes (International 10-20 system) to 256 electrodes. Electrodes are customarily placed equidistant 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 also 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 waveforms. EEG data can be processed after data collection into

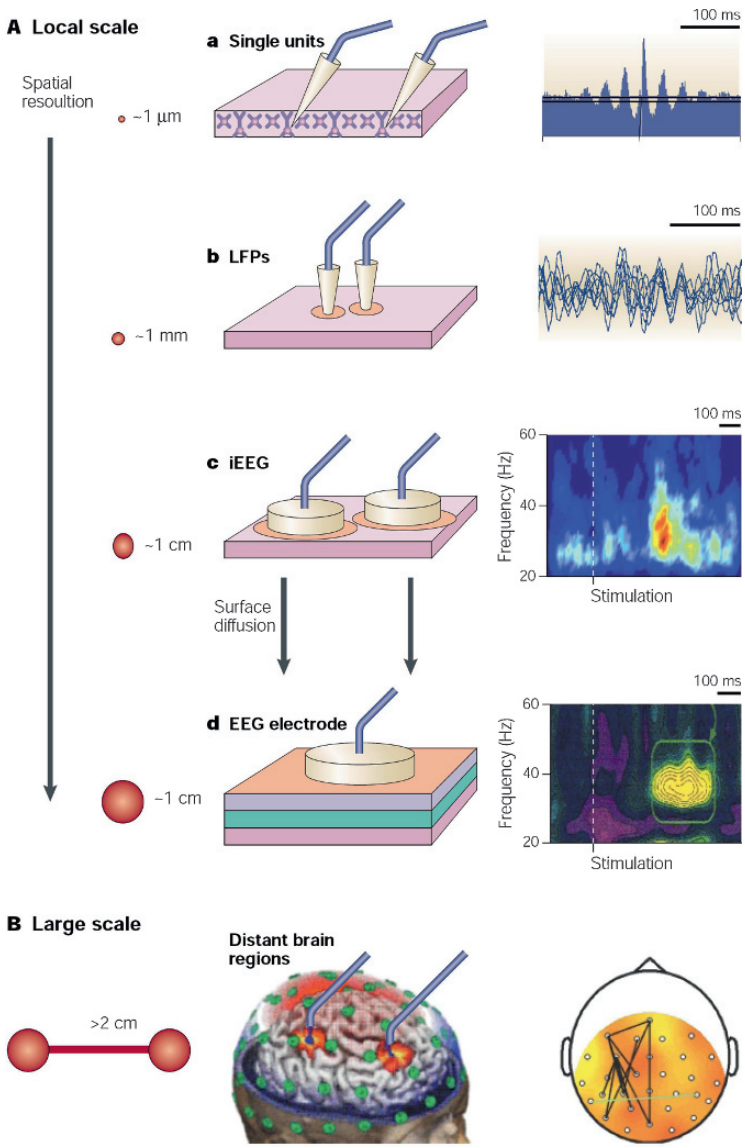

FIGURE 38.1. Neural synchrony as a multiscale phenomenon. A. Local scale: within a small brain region or local network, at least three levels of analysis can be distinguished. a) Synchrony between single units in monkey area V1 stimulated by a drifting grating, as measured by a cross-correlogram. b) 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, Varela et al., The brainweb: Phase synchronization and large-scale integration, 2(4):229–239, copyright 2001

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 the 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.

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 1965 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 306 channels, and prototype systems may soon contain up to 500 channels. 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. The experimental setup for MEG mirrors EEG, in that MEG data is detected, amplified, converted from analog to digital, and transferred to computers for further processing.

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, that, 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, nonbrain 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), as well as other sources of unwanted magnetic contamination (lights, elevators, traffic, etc.). The spectral frequency of these noise sources overlaps completely with that of the brain, so 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, and must remain very still during the study, which may be brief (40 s) or lengthy (1 hour). Because the neuromagnetic signal drops off with 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 superconducting 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 transparent (not blurred by the skull and scalp, as is EEG) (42). This transparency to the signal results in MEG offering better 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, thus, such recordings are less patient friendly. 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 opening of the 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 signal blurring. 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.

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, which 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 postsynaptic 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 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 (48). Cortical layer 5 is considered to contribute heavily to recorded EEG potentials or MEG fields. Layer 3 also contributes to a small 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 its 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), beta (12.5–30 Hz), and 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 (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 (54–56). The amplitude of the spontaneous oscillations (10^{-12} T) is several times greater in amplitude than evoked responses (5–100 10^{-15} T) described below.

Commonly detected waveform patterns elicited at certain times and under conditions have components with named waveforms, as discussed above. 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 involves 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 . Schizophrenia patients often exhibit less habituation to the second click (57). The P or N part of the component name refers to the polarity of the electric potential signal, which may be displayed in EEG with either negative or positive direction up. As illustrated above, an MEG channel does not have a reference, thus, 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.

1.4. Data Analysis Methods for EEG and MEG

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 nonbrain 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 losing trials. 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 (58, 59).

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 (60). 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 (61).

Muscle artifacts can also obscure brain data, therefore, subjects are encouraged to relax their muscles. Movement artifacts are more troublesome for MEG, and data acquired during 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 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 (62, 63).

Environmental electromagnetic noise is pandemic. Some metal orthodontic appliances, such as braces or built in retainers, introduce a 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.

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 jitter across the single responses from the brain and the jitter in noise sources (e.g., cardiac artifact) across trials, simply cancelling in the averaging process. The term "grand average" refers 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 (64). 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 90% or greater goodness-of-fit criteria, 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. 1.4.3).

1.4.3. Out-of-Phase E/MEG "Induced" Responses

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 (65). One method of studying ERD/ERS uses temporal spectral evolution (TSE) (66). 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.

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 have subtend over a spatial region—unlike a point source—when analyzed with a distributed model. Again, *it is still the same data*, *whether modeled as tiny points or large blobs* . Intracranial responses often identify a large area of neurons participating in a task (e.g., language (67)), thus, the distributed models are probably closer to reality. Just how the boundaries of active areas are defined is an active area of 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 never makes inappropriate estimates of activated volumes. Because not all responses are dipolar, such as induced responses, ECD models do not include nondipolar activity.

Noise or large neural sources are sometimes "removed" from the data through signal space projection methods (68), thereby modeling weaker sources successfully. 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 (69). Originally, all neural sources with beamformers had to be considered uncorrelated with one another (70), but this approach now has many variants, with one permitting correlation of neural sources (71). Some source analysis methods, such as the Minimum Norm Estimate (72) or Minimum Current Estimate (73), constrain source location largely to the cortex, but these methods too have variants, such as the depth-weighted Minimum Norm Estimate (74). Other data analysis approaches include more Bayesian methods. The plethora of analysis approaches can easily overwhelm the reader. The main aspects of analyses are: 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).

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 can also reveal the "when" (timing) and, in many cases, such as the cortex, the "where" of active populations of neurons. Below, are listed a few examples of the topics that can be investigated with neurophysiology.

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 (75). In a study of arithmetic tested using videotaped presentations of puppets, Berger and Posner (2006) 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 (76). Rojas's MEG study of auditory processing in children and adults illustrates the dynamic nature of the brain's auditory response (77). Differences in EEG topography related to the processing of errors are more evident between adults and adolescents with increased task difficulty (78). Aine et al. (79) found measured patterns of neuromagnetic responses in young and elderly adults during memory tasks for six brain regions during recognition and encoding.

1.5.2. Perception and Cognition

Neurophysiological recordings can aid in understanding information processing. An MEG study of pain by Forss et al.

(80) detailed different time courses for neural correlates of pain information carried by two different pain fiber pathways. Intracranial recordings of human ventral occipitotemporal cortex by Allison et al. identified a larger patch of cortex responsive to face stimuli in the right hemisphere versus the left for the N200 response (81). 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 (82) and reduced N400/N400m (83, 84) 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 (85) and fragile X syndrome (86).

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 (87). 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. measured dramatic reductions in the amplitude of evoked potentials in young children (7 to 32 months of age) who had been institutionalized at very young ages when compared with never-institutionalized children of the same age (88). However, in adults, increased range in ERP to socially positive (grade of an A) versus socially negative feedback (grade of an F) was found in depressed patients as compared with control subjects.

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 may be more costly. Nevertheless, as revealed in the following subdivisions, these integrative approaches yield important, unique insights.

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., fMRI neuroimaging provided the constraint on source location to enable modeling of the time course of MEG neurophysiological responses in orbital frontal cortex (OFC) (89). 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 location modeling of MEG data from the OFC. This area is difficult to assay with MEG alone because OFC is located behind the eyes, which are 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.(90) combining EEG and ^{18}F–FDG, PET measurements were made of depressed patients and control subjects 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. revealed parallel time courses of activation in ventral and dorsal visual pathways (91). Of note, care in interpretation becomes important since when one signal increases, such as BOLD, another signal, such as alpha frequency, may decrease (92).

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 (93). In an ERP study, Johnson et al. found the P300 waveform component (hypothesized to reflect attentional and working memory resources) amplitude depended in part on the specific polymorphism of the cannabinoid receptor gene (94). Using MEG, Cañnive et al., noted differences in control subjects based on catechol-O-methyltransferase (COMT) polymorphisms in the M100 ERF gating patterns to pairs of auditory clicks (95). 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.

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 $I_\circ$ passes through the body, becomes attenuated, and gets detected with intensity I. The definition of attenuation coefficient, μ, follows:

$$I/I_\circ = e^{-\mu x},$$

where x is the thickness of the body through which the x-ray passes. In reality, different tissues within the body have different thicknesses and attenuation coefficients. 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. On most CT units, the image brightness and contrast depends on a CT number defined as:

$$\text{CTnumber} = 1,000(\mu - \mu_w)/\mu_w,$$

where μ_w 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 CT numbers is termed reconstruction. The typical radiation dose for a CT scan of the head is approximately 3 to 5 rad. The typical attenuation scan from modern PET scanners are, in essence, CT scans.

3. Magnetic Resonance Imaging

The magnetic properties of oxygenated and deoxygenated blood have been known since the 1930s (96). 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 (97, 98), and the discovery, two decades later, that the application of imaging gradients in addition to a static magnetic field could provide localization of signal (99, 100). MRI became clinically applicable in the 1980s (101), providing a wide range of contrast mechanisms for visualizing soft tissue and tissue properties such as perfusion.

For most MRI scans, the signal comes from hydrogen nuclei (protons) on water molecules, which possess intrinsic magnetic moments and, therefore, interact with the strong magnetic field of the MRI scanner. A radio frequency (RF) excitation pulse is used to create a detectable magnetic resonance (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 regarding 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 (102–105). Although 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.

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, similar to 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 with each adding 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 difference between the magnetic field in and around veins and the magnetic field in fully oxygenated tissue is the source of the BOLD signal.

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. (106), visual stimulation 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 a flashing LED stimulus was alternated against 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 (i.e., increased with respect to rest). 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 a net increase, of local deoxyhemoglobin was the result of visual stimulation.

The positive BOLD signal was not surprising in view of PET studies that had shown an apparent overcompensation of blood flow in response to brain activation (107). At rest, the blood in arteries is fully oxygenated and venous blood is approximately 60% oxygenated. The cerebral metabolic rate of oxygen consumption ($CMRO_2$) only increases by approximately 5% during focal neural stimulation, whereas 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 an increase venous oxygenation during stimulation. Thus, the net BOLD response to stimulation is typically an increase in signal intensity caused by a reduction in venous deoxyhemoglobin concentration.

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. Although variations will be discussed below, the typical BOLD hemodynamic response is described here. After a brief neural stimulus, blood flow begins to increase after a delay of 1 to 2 s. 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 (108, 109). The latency is also longer in large veins than it is in small veins (110), but an average response will peak 5 to 6 s after stimulus onset. If the stimulus is sustained, as in a block design experiment in which stimuli are presented continually for 10 or 20 s, 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, thus, 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 poststimulus undershoot that lasts approximately 10 s (again, this is dependent on the individual subject and details of the stimulus) before the hemodynamic response recovers 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 (111). This model separately considers the following contributions to the hemodynamic response:

1. Oxygen consumption. The metabolic demand of presynaptic and postsynaptic activity and generation of action potentials in neural communication results in increased demand for oxygen. Of these different aspects of neural coding, postsynaptic activity and integration of dendritic information are predicted to be the most metabolically demanding (112) and, therefore, most tightly coupled to the hemodynamic response. Although 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 metabolic demand must be met by increased blood flow. Mechanisms of neurohemodynamic coupling are not fully understood, but some combination of nitric oxide (113), extracellular potassium ions (114), and/or glutamate (115), and direct innervation of smooth muscle cells (116) results in an increase in blood flow (and, therefore, local supply of glucose and oxygen) when neural activity increases.
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% (103). A combination of delayed venous compliance (117) and reduced deoxyhemoglobin concentration generates the poststimulus undershoot in the BOLD signal.

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 (118), subsequent imaging of columns using fMRI techniques, (119, 120), and the observation of control points strategically positioned on small arteries and capillaries (121). BOLD contrast, however, originates from changes in deoxyhemoglobin concentrations in veins, which can pool signal from multiple arterial control points. As imaging technologies improve and become capable of acquiring higher-resolution images in shorter times, it is important to understand whether the underlying BOLD signal has the same spatial resolution as the image.

The majority of BOLD fMRI studies use gradient echo BOLD. The term gradient echo (GE) refers to the pulse sequence, which determines how the image data are collected. A 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 cortex 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 (122–125). Large veins pool signal from a relatively large region of cortex ($\sim$5 mm in diameter), which is acceptable for studies that do not require high resolution. 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 GE pulse sequences, spin echo (SE) pulse sequences use an additional radio frequency 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 (0.5 - 3.0 Tesla, the magnetic field strength of typical clinical scanners), the fact that the signal is refocused in venous blood (intravascular effects) means that SE-based BOLD fMRI offers no advantage for spatial resolution. However, at very high magnetic fields, the short T_2 of blood (compared with the tissue (126)) erases the intravascular contribution of large veins. Thus, SE BOLD at 7 T is primarily sensitive to capillaries and small intracortical veins (127). The concomitant reduction in contrast-to-noise ratio (128) 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 ultrahigh-field fMRI is one reason that a growing number of research sites are installing commercially produced 7 T scanners.

3.1.4. Challenges for Functional MRI

Although 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 SNR in inferior regions of the brain. Acquiring an accurate MRI scan, particularly with the types of images 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. However, 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 caused by through-slice dephasing. Distortion arises because signal localization in most MRI studies 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 scan, it is possible to correct for distortions before analyzing functional data (129). Adding such a postprocessing step can greatly improve the accuracy of signal localization in fMRI studies.

In addition to distortion caused by frequency offset errors, fMRI images suffer from signal loss because of 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 precesses 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 intravoxel dephasing of the spins. Although postprocessing 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 (130, 131). Although 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 GE EPI.

3.2. Perfusion fMRI

Perfusion fMRI experiments measure 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 (132–136).

3.2.1. Technique

Whereas 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 to 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) on the order of 1,000 ms. It is this longer time scale 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 ms. The longitudinal magnetization in the tagged, or labeled, blood has not recovered to equilibrium values after this delay, thus, 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, measured by 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 often less than that of BOLD techniques, despite the large signal modulation inherent to the technique.

3.2.2. Advantages and Limitations

The great advantage of perfusion fMRI is that it circumvents the venous blurring that is central to concerns regarding 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 limits how quickly data can be acquired; the need for both labeled and unlabeled images to calculate perfusion from subtraction further increases the minimum time required to acquire a volume of data. Many block design experiments, however, can tolerate this relatively low temporal resolution.

3.3. Anatomical MRI

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 regarding 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.

3.3.1. Structural Imaging

Where 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 most commonly the 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 (137, 138) and to increase the field strength (139). Although 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, thus, 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 RF coil used to receive the signal, but also the bandwidth of the receiver and the speed of the imaging gradients, thus, there are no hard and fast rules regarding 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 (140). On a microscopic scale, MRI scans can detect the formation of Alzheimer's disease plaques in mouse models of the disease (141), 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 syndrome (142), decreased hippocampal volume in depression (143), and progressive loss of gray matter in schizophrenia (144).

3.3.2. Diffusion Tensor Imaging

Although 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 origin of BOLD in SE 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 (145). Spins (protons on water molecules) with small diffusion constants 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 intravoxel 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 CSF. In white matter, however, the myelination of the axons and the bundling of axons into fascicles constrains the diffusion of water molecules. 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 (146) and axon degeneration in multiple sclerosis (147), 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 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 region of the brain might have strong anatomical connections with the seed region. An active area of research considers the correct computational approach to take when two bundles of axons cross each other, resulting in a voxel that has a low fractional anisotropy despite 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 (148).

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 (149). Intraregion 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 (150).

3.4. Spectroscopy

Although 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 does so 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 (151) or disease (152, 153).

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. fMRI may be used clinically to compare brain activation during cognitive or emotional tasks. In 2004, Hugdahl et al. (154) (Fig. 38.2) found different cortical activation patterns during mental arithmetic for three groups (healthy, depressed, and schizophrenia subjects). 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. MRI is ensured a place in the neuroscientist's and clinician's

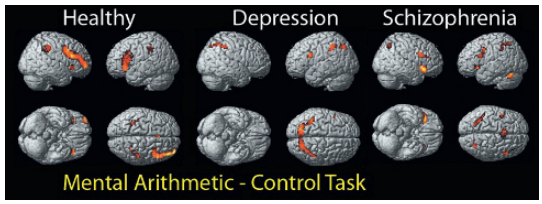

FIGURE 38.2. Unique patterns of fMRI brain activation during mental arithmetic (minus control task) were detected across healthy, depressed, and schizophrenia subject groups. Composite figure created from Figures 2,3, and 4 in Hugsdahl et al. (154). Reprinted with permission from the American Journal of Psychiatry, Copyright 2004. American Psychiatric Association.

toolbox as increasing field strength and faster parallel imaging methods enable higher resolution and better contrast.

4. 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 in a new era in medicine. Both instrumentation and novel techniques are advancing rapidly. This progress comes in part from the development of CT, so greatly dependent on 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 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, SPECT and 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 regarding radiation exposure and its effects on the body.

4.1. Radiation Exposure

Although highly sensitive with capability for measuring subnanomolar quantities of molecules, a disadvantage of these methods arises from concerns regarding exposure to radiation. Unfortunately, the general population often lacks education about radiation exposure, and the very word "nuclear" becomes cause for alarm. Not surprisingly, the word "nuclear" has been dropped from technologies such as nuclear MRI. 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 nonstochastic (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. Nonstochastic effects include "radiation sickness," more properly termed acute radiation syndrome, which occurs when rapidly dividing cells or stem cells are exposed to high levels of radiation during a brief period of time. These are the effects experienced by survivors of atomic bombs or nuclear reactor meltdowns. 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, 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 nonstochastic processes. Several units of measurement under two systems are used to quantify radiation exposure (Traditional [T] or Système International [SI]; Table 38.1). The amount of *radioactivity* is measured in disintegrations per second (dps). A curie (Ci; T) is 3.7×10^{10} dps. One dps 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 on 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) × 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

TABLE 38.1. Units of measurement used frequently in nuclear medicine.

Measurement	Traditional units	Systemè International units
Radioactivity	Curie (Ci) 3.7×10^{10} dps[a]	Becquerel (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 Seivert (Sv)

[a] dps, disintegrations per second.

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 radiation 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 regarding 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, in which the doses have important nonstochastic effects. In addition, this is not the case when using radioisotopes for research in which the primary interest is not the diagnosis or treatment of a disease. The US 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 38.2. These dose limits refer only to doses arising from an experiment. Any dose for clinical purposes is not counted when computing permissible annual exposure. 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.

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 repair mechanisms can handle low-level exposure. The average person gets 22.5 rems of radiation exposure during an assumed lifespan of 75 years.

TABLE 38.2. Annual, adult radiation dose limits (rems) for radioactive drugs and procedures for research studies (21CFR361.1, US 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 38.3. 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

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 38.3 shows equivalent risks with respect to common daily activities. For example, exposure to background radiation from natural sources is approximately 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 (155). 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, although 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.

4.2. 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 Allan Cormack, to win the Nobel Prize in Physiology or Medicine in 1979. The development of modern, high-speed computers brought CT into a clinical reality.

The concepts developed by Sir Hounsfield received broad application in nuclear medicine. They served as the foundation for both SPECT and 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 CT 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 of this chapter. Suppose someone has severe myopia, and their eyeglasses 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 on 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. A collimator, akin to a pinhole in paper to correct for lens distortion, enables the acquisition of a projection.

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. It is possible to project the radioactivity of f(x,y) using rays that are parallel and perpendicular (termed lines of response at angle θ) onto line l. The result is a function p(θ,r), p for profile, whose ordinate is the integrated radioactivity (i.e., counts per time interval for the cylinder of tissue) projected along the rays perpendicular to l. In other words, p(θ,r) represents the counts taken from projecting the object's emissions along lines of response at position r and at angle θ. How this is done differs fundamentally between SPECT and PET, and is discussed in the respective sections below. The origin of the l can be considered the center of the activity distribution, which is typically placed in the center of the scanner's field of view. The function p(θ,r) is called a projection profile. 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 using a gray scale rendering with no counts (black) to high counts (white) to represent all of these data plots θ on the ordinate and r on abscissa. The counts collected for each projection p(θ,r) are represented by the intensity of the line at that 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.

One sinogram contains 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(θ,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. 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 with 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 on the differences. As this difference decreases, the algorithm converges to a final reconstructed image.

4.3. 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. 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 after 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. One such device is termed a rectilinear camera because the gamma camera follows straight lines systematically in a rectilinear pattern over the body.

CT 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.

4.4. 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., millimeters) and is the distance between x_1 and x_2. 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 space features (e.g., point sources) in an image. Two features that are spaced apart less than the FWHM (less than x_2 minus x_1) will not be resolved as two features, but rather as one blurred feature. If the features are further apart than x_2 minus x_1, then the peaks of the two normal distributions will be detectable because the features will be resolved. The FWHM directly affects the appearance of the image through a partial volume effect, which is explained below.

The sampling theorem states that to recover spatial frequencies of an object up to a maximum of γ_{MAX} requires sampling spatially 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 postprocessing 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 to varying degrees, producing a continuous range of activities when, in reality, only two activities are present (i.e., that for white and grey matter; Fig. 38.3 and Color Plate 12, following p. 650). In reality, if the instrument had high resolution, the grey and white matter would be clearly visible, as in structural MRI. Grey matter has four times as much blood flow or glucose metabolism as white matter, thus, the grey/white matter border should have clear contrast. 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.

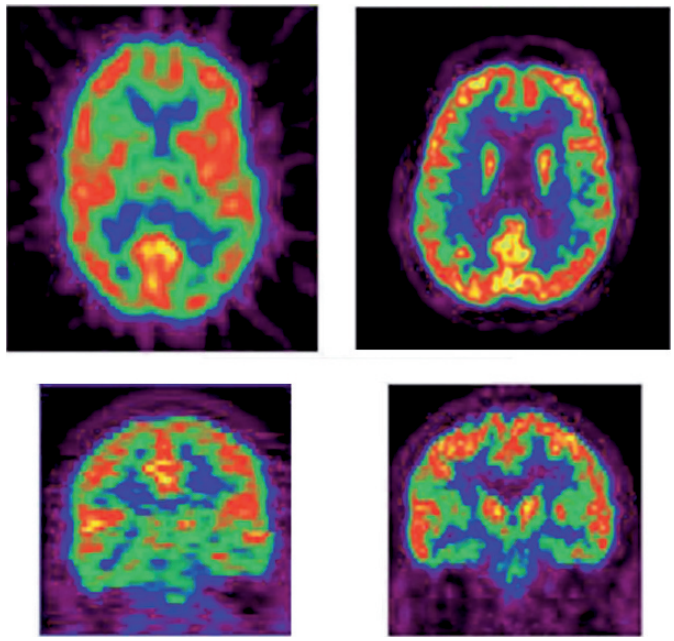

FIGURE 38.3. The appearance of partial volume effects in PET images. Grey matter is fourfold as metabolically active as white matter. The *top* panel shows two transverse sections of an FDG image obtained on an older instrument, Siemens ECAT 953B, and reconstructed to a final image resolution of approximately 10 mm FWHM (left) and an FDG image from another patient, taken at approximately the same levels, obtained on a more modern instrument, Siemens Biograph 16 PET/CT, and reconstructed to a final image resolution of 5 mm FWHM (right). The *bottom* panels shows coronal sections from the same patients using the Siemens ECAT 953B (left) and Siemens Biograph 16 PET/CT (right). The *left* panels shows blurring of the activity in grey matter, white matter, and ventricles. The *right* panels shows essentially only the grey matter ribbon, whereas the white matter and CSF are at the lower end of the color scale (blue/black). There is still some green at the interface between grey matter and white matter from some residual partial volume effects. (*see* Color Plate 12, following p. 650).

4.5. Single-Photon Emission Computed 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 CT (e.g., Sect. 2). 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 single gamma camera) or multiple heads could rotate 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, and, 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. 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 because of scattered radiation. These issues directly affect SPECT images.

The use of collimators gives SPECT some inherent 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. In addition, the resolution decreases with distance from the camera. Some of these problems have only partial solutions.

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 to 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 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 (this is discussed further in Sect. 4.7.3). 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 inherently 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.

A major advantage of SPECT concerns the ready availability of medically useful radioactive substances that emit single photons. The most widely used radioisotope for SPECT is ^{99m}Technetium (^{99m}Tc), which has a half-life of approximately 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 ^{99m}Tc generator kit that is delivered on a weekly basis. Such a generator has parent–daughter atoms (e.g., ^{99m}Mo/^{99m}Tc) 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 on the molecule attached to ^{99m}Tc, this radiotracer can be used in a variety of applications. For example, ^{99m}Tc-sestamibi is used routinely in the clinical setting for the assessment of myocardial perfusion. Assessment of cerebral perfusion uses ^{99m}Tc-HMPAO (hexamethylpropylene-amine oxime) or ^{99m}Tc-ECD (*N*,*N*′-1,2-ethylenediyl-*bis*-L-cysteine diethylester). In medical centers without ^{18}F–FDG PET, ^{99m}Tc-HMPAO is used because brain perfusion is coupled to brain metabolism.

SPECT has several advantages beside lower cost, greater availability, and convenient radiotracer generation. For example, if a patient has a seizure, the ^{99m}Tc-HMPAO can be quickly injected. Once bound in the brain, the half-life permits subsequent scheduling and transportation to an imaging center. Likewise, brain perfusion imaging is possible during different stages of sleep by injecting ^{99m}Tc-HMPAO through a venous catheter at a time when EEG 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 for imaging. The logistics of a similar study with FDG PET are more difficult and demanding.

SPECT is used in studies of brain receptors, neurotransmitters, and other molecules relevant to psychiatry (156). Unlike in vitro ligand binding assays, in which 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, SPECT receptor assays typically only determine the *binding potential*, a hybrid measure that 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 one can not usually administer high concentrations of cold ligand to displace 50% of the radiotracer—the usual way to measure Bmax and Kd. Such drug concentrations would have pharmacological side effects and toxicity.

Two modifications are used to obtain the true Bmax and Kd, although not without an increase in complexity and cost. The first methods is a multi-injection protocol (157, 158). The volume of distribution (Vd) is the ratio of the concentration of the tracer in the brain divided by the concentration of tracer

in the plasma at equilibrium. Except for some corrections (such as the tracer concentration in the plasma within the brain tissue and the amount of nonspecific binding in the brain), Vd approximates the ratio of bound tracer to free tracer, which is the required dependent measure to perform a Scatchard plot analysis used to derive Bmax and Kd. The brain tracer concentration can be estimated from the amount of activity measured by the SPECT scanner, whereas the plasma concentration can be measured through blood sampling. In practice, after a loading dose, a continuous infusion of radiotracer is adjusted until the activity in the brain becomes constant. Note that ligands with extremely high affinity may not work in this method because the activity in the brain will never become constant but will continue to increase, and no reasonable amount of time will lead to equilibrium. Under steady-state conditions, the input of radiotracer matches the efflux of radiotracer out of the brain. Because a Scatchard plot requires two measurements of bound/free ligand, the study can be repeated with a different level of receptor occupancy through infusion of cold ligand.

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 (159). Note that both of these methods minimize the impact of SPECT's approximate corrections for attenuation and scatter because any inaccuracies would occur in both SPECT scans used in the Scatchard analysis. If only a single scan were required, these deficiencies of SPECT would be of greater concern.

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.

4.6. Positron Emission Tomography

4.6.1. Tracer Production

Most positron emitting radiotracers are made in a cyclotron. Ernest O. Lawrence (1901–1958) conceived of the cyclotron principle in 1929. He, along with MS 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 "dees" (because their shape is like the letter "D" separated 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. 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. On 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.

4.6.2. 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 be 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, 1,720 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.

Oak Ridge Institute for Science and Education (ORISE) 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 the Medical Internal Radiation Dosimetry (MIRD) committee. This estimate of radiation dose needs to be calculated for the proposed dose to ensure the exposure is within FDA limits for research.

Because SPECT is essentially a gamma camera, why not use a PET camera to image radiopharmaceuticals that emit only a singe photon? PET cameras are not equipped with mechanical collimators. In addition, 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.

4.6.3. 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 nanoseconds). 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 were discussed above (Sect. 4.3), 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 with 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 nearly 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 coincidences.

4.6.4. Instrumentation

The first positron device was invented in 1951 independently by two groups: William H. Sweet (160) at Massachusetts General Hospital, and Phillip Handler (161) 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 CT by Hounsfield, a group at Washington University led by Michelle Ter-Pogossian saw the great potential of applying this early technology for non-invasive imaging in humans. The first multicrystal scanner was invented in 1975 by Drs. Ter-Pogossian, Phelps, and Hoffman (162, 163). Thereafter, progressively greater number of detectors and multiple rings of detectors brought the technology to maturity. Improvements in crystal technology led to the latest, most 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.

4.6.5. Applications of PET

4.6.5.1. Tracer Kinetic Modeling

SPECT and PET provide tools to measure the amount of a radioactive substance in the brain non-invasively using emission CT. 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 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, is used to measure brain blood flow. FDG, 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 as well as hexokinase. However, after 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 National Institutes of Health (NIH) (164, 165). 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: a vascular compartment, a "free" compartment in which FDG is in the tissue but not phosphorylated, and a metabolic compartment in which the glucose or FDG is phosphorylated. Third, the kinetics of movement between compartments 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 kinetics, the radioactivity measurement obtained from SPECT or PET can be converted into a quantitative physiological parameter. Likewise, SPECT measurement of a ligand bound to the brain can be used to calculate using modeling Bmax and Kd.

4.6.5.2. Brain Blood Flow

The development and application of neuroimaging arose from pioneers in psychiatry in their search for answers to questions regarding consciousness and disorders of the mind. Seymour S. Kety (1915–2000), although neither a psychiatrist nor a neurologist, realized the importance of quantitative measurement of brain blood flow and metabolism to study the mind: "But to me, the most interesting information is the finding that in a large group of mental states markedly different from normal there is no significant deviation in cerebral oxygen consumption (166)."

He, in collaboration with Carl Schmidt, pioneered the measurement of brain blood flow based on the Fick Principle (167): the quantity of a substance taken up by the brain during time T (mole/minute/kilogram tissue) is the time integral of the difference between the arterial (carotid artery) and venous (internal jugular bulb) concentrations (mole/liter) multiplied by the brain blood flow (liter/minute/kilogram tissue). Kety reasoned that a freely diffusible inert tracer such as N_2O could be used. Then, deriving several dependent measures permits calculation of CBF: N_2O concentration difference between arterial and venous samples over time, $\Delta AV(t)$ (mole/liter); brain volume, V (liter); and brain weight, W (kilogram). 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:

$$CBF = VS/\int \Delta AV(t)dt.$$

The sharp contrast in blood flow between grey and white matter is clearly visible. This work presaged the future development of techniques permitting non-invasive autoradiography in humans using emission CT.

In 1983, Huang et al. (168) and Raichle et al. (169, 170) 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. (171) 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 s (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 blush 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 (172). 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) became routine. Differences between images enabled isolation of the cognitive process under study. The short half-life of ^{15}O-labeled water (~2 minutes) meant that, 10 minutes after a snapshot, another scan was possible. Additionally, the brief imaging period (40 s; neurovascular response time, 6–10 s) minimized habituation and learning effects during the actual scan.

4.6.5.3. Brain Glucose Metabolism

Along with the development of methods for measuring CBF, Louis Sokoloff and colleagues developed the deoxyglucose technique (164, 165). Glucose provides 95 to 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 use 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 during the first 15 to 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 regarding the optimal state under which the subject should be studied. Frequently, the state is resting with eyes closed. At first, this may seem very uncontrolled, but, in actual fact, this state is very reproducible and may reflect a default-mode, idling state (173). Some also use an easy vigilance type of task, such as the continuous performance task (CPT). 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 regional CBF (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 to 20 minute scan is normalized to a fixed value to account for slight differences

in injected radioactivity or intersubject 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 SNR (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.

4.6.5.4. 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.

TABLE 38.4. 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]β CIT	SPECT	DAT
[^{11}C] WIN 35428	PET	DAT
[^{18}F]FECNT	PET	DAT
[^{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	α4β2 nACHR
[^{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	Mu-opiateR
[^{11}C]deprenyl	PET	MAO-B
[^{11}C]clorgyline	PET	MAO-A

Some of the radiotracers used in psychiatric studies are listed in Table 38.4. 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.

Multimodal approaches offer particular promise. For example, PET has been combined with fMRI. In one such study (174), PET was used to measure $5HT_{1A}$ 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 that a reduction in inhibitory $5HT_{1A}$ autoreceptors in the raphé, i.e., diminished capacity for autoinhibition of serotonin release, was associated 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 $5HT_{1A}$ binding in the amygdala explained little of the variance. Furthermore, mouse knock-outs of the $5HT_{1A}$ receptors lead to an anxiety-like syndrome (175). Such work begins to identify neuromodulatory mechanisms at the level of systems neuroscience. This research bears directly on 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 (176). In this study, an oligonucleotide complementary to the messenger RNA (mRNA) of c-Fos, a marker of neuronal activation, was coupled to superparamagnetic iron oxide nanoparticles, which 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, using MRI, Liu et al. (166) demonstrated, in live rats, increased binding of the probe after 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 amphetamine. Although demonstrated using MRI, use of PET radioligands has the potential for even greater sensitivity. Such technology portends that in vivo, non-invasive, imaging of human gene expression is in the not too distant future. This ability will be particularly important in psychiatry, in which diseases have complex genetics with strong environmental effects, thereby modulating gene expression.

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39
Electroconvulsive Therapy: Indications, Use, and Adverse Effects

Suck Won Kim, MD and Jon E. Grant, MD, JD

Abstract In this chapter, we discuss indications, pre-electroconvulsive therapy (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. The 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 wave ECT has been incorporated.

Keywords ECT · Electroconvulsive Therapy · Refractory depression · Ultra-brief unilateral pulse wave

1. Introduction

The primary goal of this chapter is to summarize clinical indications, methods of application, and unwanted consequences of electroconvulsive therapy (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 complied in this book chapter depended, in part, on that book, along with books by Maletzky (2), Fink (3), Abrams (4), and is also based on longer than 40 years of clinical application experience of ECT by the authors.

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 the intravenous line is established and pre-ECT medications are administered; in an ECT administration room, where an anesthesiologist is in charge of general anesthesia and a psychiatrist administers ECT; and in a recovery room, where nurses provide services during the recovery phase post-anesthesia.

Typically, ECT is administered three times a week for a total of eight treatments. With an advent of ultra-brief pulse wave unilateral ECT, the average treatment number is likely to increase. Unless future research findings suggest otherwise, the ultra-brief pulse wave right unilateral ECT is likely to dominate future ECT. This is primarily because of a dramatic reduction in memory loss which is consequent to the administration of the ultra-brief pulse wave 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 after a partial completion or full completion of a series of ECTs in the case of an inpatient. In the latter case, three times a week ECT is extended to once a week for 2 to 4 weeks, then the interval of ECT is lengthened to every other week and then to once a month. The patient often can pinpoint 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 (5).

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, but empirical data for the safety of long-term ECT (5–10 years or longer) are not found in the literature.

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In general, it is true that ECT is safe and effective, however, a psychiatrist who is to recommend ECT to his/her patient should not overemphasize the safety or efficacy of ECT; the failure rate of ECT is not low (6) and cardiac and other clinically significant complications do occur with ECT.

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 (7). We strongly recommend that psychiatrists try at least two MAOIs before recommending a patient for a series of ECTs.

In treating patients with refractory depression, a psychiatrist should not adhere only to those compounds with which they feel comfortable with. This means that the psychiatrist should administer each of all known selective serotonin reuptake inhibitors (SSRIs) one by one, venlafaxine, bupropion, mirtazapine, duloxetine, or trazodone, even including agents not frequently prescribed these days such as clomipramine or an MAOI before administering ECT. What this often means is that the patient goes through a few to several years without feeling any relief from their depression, because of lack of treatment by all possible agents.

For suicidal patients, ECT can be a life-saving measure. Selected catatonic patients 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 (8, 9).

Editor's note: In severe refractory cases of schizophrenia when the patient is extremely agitated or psychotic, ECT is recommended.

3. Pre-ECT Evaluation

A comprehensive medical and psychiatric history is required to ensure that there is a clear indication for ECT and that 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 (10).

Often, cardiology consultation is requested in the case of preexisting heart disease, in part, because of the known complications of ECT in patients with preexisting heart disease. In a study, Zielinski and his colleagues reported that, in 40 patients with preexisting cardiovascular disease, 15 patients developed ventricular arrhythmias, 9 patients developed ischemic events, 6 patients developed atrial arrhythmias, and 3 patients developed bradycardias. In the same study, 8 patients developed persistent EKG changes accompanied by chest pain, asystole, or persistent arrhythmias (11).

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 (12). 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 electroencephalogram (EEG) were routinely obtained but, nowadays, these or head computed tomography (CT) and magnetic resonance imaging (MRI) scans 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 loose teeth, denture, and other oral cavity problems. The ECT-induced jaw tightening can damage the tongue. Dentures should be removed before ECT.

4. Concurrent Use of ECT and Psychotropic Medications

Although there are reports that suggest that use of lithium is safe in ECT (13), there are many more reports that suggest that there is a higher risk of delirium and CNS toxicity (14, 15). 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 MAOIs 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 an 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.

5. Method of ECT Administration

5.1. Right Unilateral Ultra-Brief Pulse Wave ECT

Bitemporal electrode placement is still widely used. Advantages and disadvantages of bilateral versus unilateral ECT have also been published extensively (16, 17). 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 ECT. A dramatic reduction in memory loss is seen with this new treatment. The reader should be aware that this new method and the treatment efficacy from such a new method have not been established through published reports, except for one abstract (18).

Sackeim and his colleagues have summarized cognitive and affective consequences of right unilateral ultra-brief pulse wave ECT (18). Optimal width of a pulse stimulus to produce neuronal depolarization is in the range of 0.1 to 0.2 ms. Traditionally, however, a longer pulse duration, of 0.5 to 2 ms, has been used. The central concept here is not to deliver energy while CNS neurons are in a refractory phase immediately after depolarization.

In a new approach, Sackeim and his colleagues kept pulse frequency at 20 to 30 Hz and used treatment duration as the primary variable to manipulate dosage (up to 8 seconds, which is twice as long as the duration for the traditional bilateral ECT) (19).

They noted that ultra-brief stimulation is more efficient in seizure induction and found that memory loss was dramatically reduced when compared with the standard pulse width stimulation.

As usual, we have had difficulty inducing or maintaining seizures in some cases. In such cases, we use hyperventilation, intravenous caffeine, and/or an alternative anesthetic, such as etomidate (20). In contrast to the barbiturate class of drugs, such as thiopental or methohexital, etomidate does not raise the seizure threshold. Etomidate, however, is known to cause reversible adrenal suppression (21), and should not be used routinely.

Technical aspects of ECT administration have not been addressed in this chapter. Interested readers should refer to the *Practice of Electroconvulsive Therapy* by the American Psychiatric Association (1) for this information.

6. Number of Treatments

Typically, patients are given 6 to 12 treatments. Some patients improve dramatically only after receiving two to three treatments, whereas others do not even begin to improve until the 10th treatment. Although it is commonly thought 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% drop in this scale or less drop in this scale is defined as treatment failure, the overall failure rate reached 58% (22). In treatment nonresponsive cases, it is not uncommon to see the total number of treatments reach 15 to 20.

Known evidence, to date, indicates that there is no permanent brain damage associated with extended ECT (23, 24).

7. Adverse Reactions

Approximately 50% of patients report headache, nausea, and muscle pain. The cause of post-ECT headache is not well known. It could be caused by temporalis muscle spasm, acute increase in blood pressure (systolic pressure often reaches 200 mmHg or higher) 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); Vicodin (hydrocodone with acetaminophen: 5/500; 7.5/750; 10/660); 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 medicine. Although some think that muscle aches come from the seizure, more commonly the muscle aches are caused by fine muscle fiber fasciculations after the use of succinylcholine. Pain coming from intense seizure, however, cannot and should not be exlcuded.

Nausea is another common post-ECT side effect. A 5-HT_3 receptor antagonist, such as 4 or 8 mg ondansetron intravenously is used very often to counteract nausea just like an intravenous nonsteroidal anti-inflammatory drug (NSAID) is used to reduce headache. 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. In some cases, 2 to 4 mg intravenous midazolam (Versed) is enough but, in other cases, a stronger measure is needed. Often, 5 to 10 mg intravenous haloperidol (Haldol) or 10 mg intravenous olanzapine (Zyprexa) is needed. Ten milligrams olanzapine sublingual preparation (Zydis) before 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 postictal phase because, during this period, patients often show disturbed sensorium and poor memory. Examination is usually conducted 1 day or longer after ECT. The Mini Mental State (25) is used often.

One exception is that, with the advent of right unilateral ultra-brief pulse wave ECT, the post-ECT confusion period is significantly shortened. In the majority of the cases, confusion resolves within 1 hour, in contrast to the several hours for resolution that accompanies traditional bilateral ECT.

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 back it up.

Documented evidence suggests that concurrent use of antidepressants may augment ECT effects, and a good number of patients are taking one or more antidepressants while undergoing ECT. ECT specialists often switch to bilateral from unilateral mode and/or extend the number of ECT treatments to 15 to 20 in the absence of response. Seizure-dampening medications are double checked to be sure 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, a vagus nerve stimulator or a deep brain stimulator (12), alone or in combination with ECT, needs to be considered. In the case of vagus nerve stimulator implantation for treatment of refractory depression (26), a coil-shaped terminal is wrapped around the 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 an otolaryngologist. In the case of deep brain stimulator, a burr hole is created on 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 (27).

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 1 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 multiyear, if not lifetime of, management.

Thus, most psychiatrists continue to provide antidepressants and/or an augmenting agent after successful ECT. Despite these measures, relapse rates, among psychotic or pre-ECT drug-refractory depression patients remain high (28).

10. Continuation of ECT After Index Treatment

Continuation of ECT seems to bring out equal or better treatment outcome in comparison with pharmacotherapy (6, 29).

11. Maintenance of ECT

Maintenance of ECT is defined when ECT is extended beyond 6 months from the index treatment. A recent trend indicates that more patients are seeking maintenance ECT. Maintenance ECT has been successfully monitored (clinical observation only) for multiyear periods, 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- to 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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40
Profiles in the History of Neuroscience and Psychiatry

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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 during the next 6 years and, on 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 that 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.

FIGURE 40.1.

After 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 staining histological sections from his colleague, neurologist Franz Nissl. Alzheimer then went to work in Kraepelin's Munich laboratory, where Alzheimer 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 Alzheimer's work, we now know that both presenile (familial) 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 protein accumulation and hold potential to ameliorate the lives of patients with Alzheimer's disease. Alois Alzheimer died in 1915.

Mauer K, Mauer U. Alzheimer: The life of a physician and career of a disease. New York: Columbia University Press, 2003.

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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

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FIGURE 40.2.

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, and 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 suicidality, 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 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.

Hafner H. Laudatio in honour of Professor em Dr med Dr med h.c. Jules Angst on the occasion of the Burgholzli Award. Acta Psychiatr Scand Suppl 2003;(418):7–10.

Avicenna

Avicenna (Fig. 40.3 and Color Plate 13, following p. 650) 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 of Medicine* detailed and classified diseases, including their presumed causes. It included a description of symptoms and complications of diabetes. Additionally, hygiene, pathology, medicines, and bodily functions were described. Avicenna was the first to correctly describe the anatomy and afflictions of the human eye, such as cataracts; he emphasized contagion of tuberculosis; and described complications of diabetes and facial paralysis. Avicenna also had an interest in psychology, and wrote extensively on the effect of emotions on physical conditions. His writings also referred to topics related to insanity, melancholia, agitation, hysteria, alcoholic intoxication, and mental confusion.

FIGURE 40.3. Avicenna (*see* Color Plate 13, following p. 650).

Avicenna was born in 980 in Afshana near Bukhara. He received his medical training at age 16 years, attaining full status as a physician at age 18 years. He worked throughout his career, moving from place to place, for various governmental officials. In addition to *The Cannon of Medicine*, 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 BS 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 MA from New York University in 1941 while he was a chemist at the Laboratory of Industrial Hygiene. In 1950, he began his career at the National Institutes of Health (NIH) as an Associate Chemist in the Section

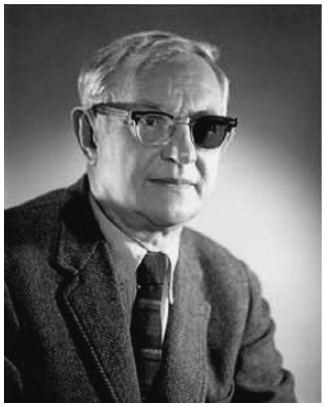

FIGURE 40.4.

on Chemical Pharmacology, National Heart Institute. From 1950 to 1953, Axelrod was a Chemist with the National Heart Institute, NIH, where 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 PhD 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 follows 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.

http://nobelprize.org/nobel_prizes/medicine/laureates/1970/ axelrod-bio.html
http://nobelprize.org/nobel_prizes/medicine/laureates/1970/press.html
A Tribute to Julius Axelrod. Cell Mol Neurobiol 2006;26(4–6).

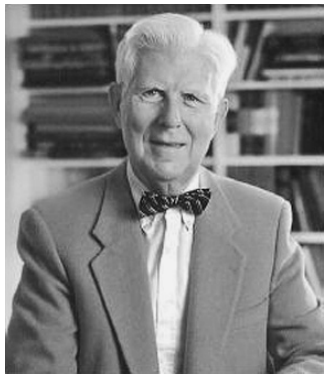

FIGURE 40.5.

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 think that depression was caused by unrealistic, negative views directed at the self, the world, and the future. Through his research in psychotherapy, psychopathology, suicide, and psychometrics, he developed CBT 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, RI 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, MA studying long-term psychotherapy and, in 1954, accepted a position in the Department of Psychiatry at the University of Pennsylvania, where he continues his research to date. His work on prevention of suicide with short-term CBT has been funded by the M.E.R.I.T. Award from the National Institutes 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.

Beck AT. Depression: Causes and Treatment. Philadelphia: University of Pennsylvania Press, 1972.
Center for the Treatment and Prevention of Suicide, University of Pennsylvania; A Biography of Aaron T. Beck, MD. http://mail.med.upenn.edu/abeck/biography.htm

Paul Eugen Bleuler

Bleuler was a Swiss psychiatrist most notable for his contributions to the understanding of mental illness and the naming

FIGURE 40.6.

FIGURE 40.7.

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 that 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, thus, 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 he described schizoid personality.

Bleuler E. Dementia Praecox. Madison, CT: International University Press, 1950.
http://www.answers.com/topic/eugen-bleuler

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 Camilio Golgi, Ramón y Cajal's work led him to postulate that the nervous system is made up of millions 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 he received his licentiate in medicine at the University of Saragossa in 1873. He later received his doctorate of medicine at Madrid, and he was appointed as a university professor at the University of Valencia. He later had professorships in Barcelona and Madrid, and he 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, on his retirement in 1922. During his career, Ramón y Cajal published more than 100 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 Camilio Golgi. He died in 1934.

http://nobelprize.org/nobel_prizes/medicine/laureates/1906/cajal-bio.html

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

FIGURE 40.8.

FIGURE 40.9.

areas of the brain that control walking and voluntary movements. He discovered that levodopa, can be used to make dopamine in the brain, 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 thought. Carlsson's research led to our current understanding of the relationship between neurotransmitters and mental disorders such as schizophrenia and depression and, ultimately, led 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.

Carlsson A. Autobiography. Nobelprize.org.

Erminio Costa

Erminio Costa was born in Cagliari, Italy in 1924. His long career in scientific research began in 1947, when he earned his MD 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 Laboratory 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 was Professor in the Departments of Anatomy and Cell Biology and Pharmacology at Georgetown University, Washington, DC until 1994. Since 1996, Erminio Costa has been the Scientific Director of the Psychiatric Institute and Professor of Biochemistry in Psychiatry, University of Illinois at Chicago, Chicago, IL.

Erminio Costa's professional research activity spans over the last 60 years, and he has spent several decades studying the pathophysiology and treatment of schizophrenia and other mental disorders starting with 1) pioneering studies on the identification and measurement of serotonin in the human brain of healthy 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.

Salmoiraghi GC, Lajtha A. Foreword: In honor of Erminio Costa. Neurochem Res 1990;15(2):103.

Jean-Étienne Dominique Esquirol

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 thought 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, for whom 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

FIGURE 40.10.

FIGURE 40.11.

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 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 of people within the asylums, epileptic patients were distinguished from insane patients.

Goldstein J. Console and Classify: The French Psychiatric Profession in the Nineteenth Century. Cambridge: Cambridge University Press, 1987.

Weiner D. Le geste de Pinel: Psychiatric myth. In: Micale MS, Porter R eds. Discovering the History of Psychiatry. Oxford: Oxford University Press, 1994:232–247.

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 the tobacco mosaic and polio viruses. Her significant contribution to the discovery of DNA structure has affected 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 the time span of 4 years, Franklin published five papers on coals and carbons, and eventually that work earned her a PhD 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 United States, 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 30, 1958 and died on April 16 of the same year from ovarian cancer.

McGrayne SB. Nobel Prize Women in Science. Their Lives, Struggles, and Momentous Discoveries. 2nd ed. Chapter 13. Washington DC: Joseph Henry Press, 1998.

http://en.wikipedia.orh/wiki/Rosalind_Franklin

Daniel Carleton Gajdusek

Gajdusek is an American physician and medical researcher, who was the co-recipient (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 MD 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 there that 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 DC. Degenerative disease of the central nervous system in New Guinea; the endemic occurrence of kuru in the native population. N Engl J Med 1957;257(20):974–978.

FIGURE 40.12.

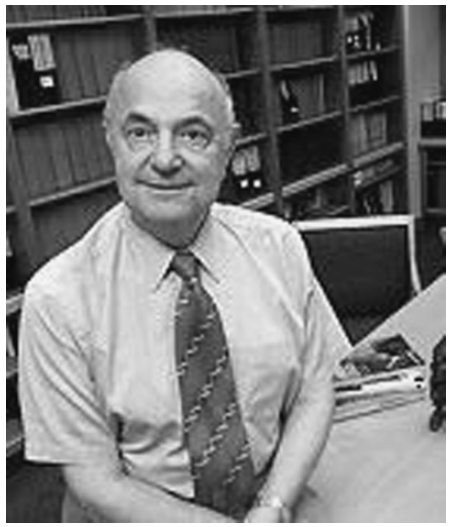

FIGURE 40.13.

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. Irving 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 have 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, Irving 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. Irving 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, recently, the Gold Medal of the American Psychological Association.

http://www.psych.umn.edu/people/faculty/gottesman.html
http://www.apa.org/monitor/julaug01/people.html
www.iit.edu/colleges/psych/alumni/newsletters/fall04.pdf
Gottesman II. Schizophrenia genesis: The origins of madness. New York: Freeman, 1991.

Paul Greengard

Paul Greengard is an American neuroscientist and professor of molecular and cellular neuroscience at Rockefeller Univer-

sity 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 and activating 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 the 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.

Greengard, Paul. Autobiography. Nobelprize.org.

Rockefeller University, http://www.rockafeller.edu/labheads/greengard/greengard-lab.html.

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 *Diagnostic and Statistical Manual of Mental Disorders*, 3rd edition (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 regarding 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 years 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 in psychiatry beginning in 1955. He served as Vice Chancellor 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 to 1997. Throughout his career, Guze received many awards and honors, including the Gold Medal Research Award from the

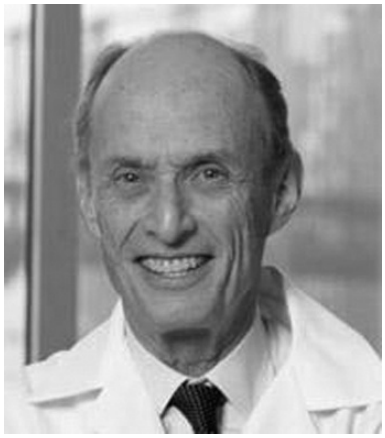

FIGURE 40.14.

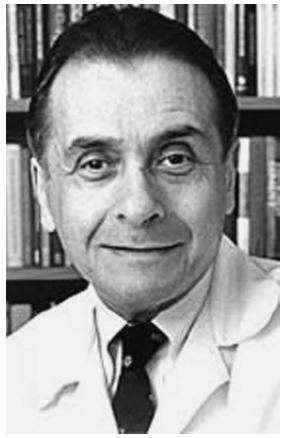

FIGURE 40.15.

Society of Biological Psychiatry and the Distinguished Public Service Award from the United States Department of Health and Human Services. He died in 2000.

Cloninger CR, ed. In Memoriam-Samuel Barry Guze (October 18, 1923–July 19, 2000). Ann Clin Psychiatry 13(1):1–10.

Paul Janssen

Paul Janssen was a Belgian pharmacologist who, along with his research team, developed more than 70 compounds, most notably, haloperidol. Haloperidol, first introduced in 1959, has remained, 40 years later, one of the most effective and reliable substances to treat schizophrenia and manage psychosis (1). After the development of haloperidol, Janssen and his research team developed another 13 neuroleptics, 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. After graduation, Janssen worked as a medical 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 years, 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.

Müller N. Obituary to Prof.h.c. Dr. Drs.h.c. mult. Paul Janssen. Eur Arch Psychiatry Neurosci 2004;245:55–56.

Ban TA. Paul Adriaan Jan Janssen, 1926–2003. Neuropsychopharmacology 2004;29:1579–1580.

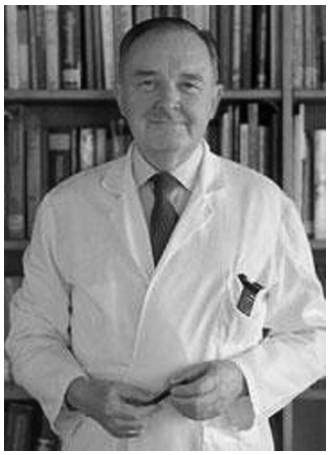

FIGURE 40.16.

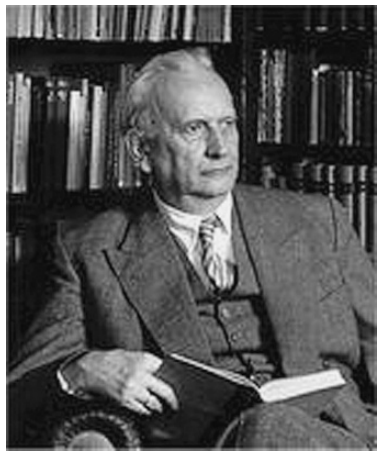

FIGURE 40.17.

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 Heidelberg, Germany, where Emil Kraepelin had worked a few years earlier. In 1913, Jaspers left clinical practice to take a post teaching psychology at Heidelberg University. At age 40 years, 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.

Jaspers K. On My Philosophy. 1941.

Eric R. Kandel

Eric Richard Kandel is an Austrian born American 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 co-recipients 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 A (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, whereas long-term memory is associated with protein synthesis and change in the number of synaptic connections.

Kandel was born in 1926 in Vienna, Austria. 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 regarding unconscious mental processing offered by psychoanalysis rooted his interest in the biology of motivation and memory. 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 Institutes of Health and at the Institut 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.

Kandel ER. Autobiography. Nobelprize.org.
Howard Hughes Medical Institute Kandel Wins Nobel Prize. Research News, October 09, 2000.

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 schizophrenic patients 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

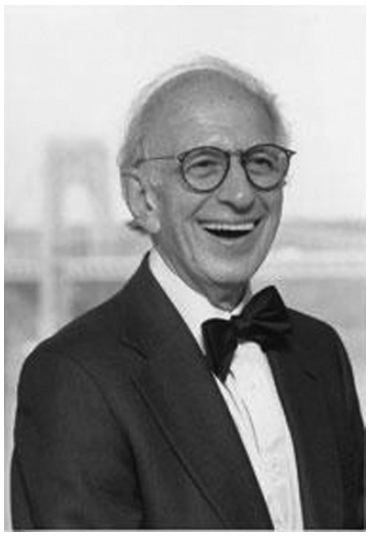

FIGURE 40.18.

FIGURE 40.19.

the National Institute of Mental Health (NIMH), despite his not being a psychiatrist, 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 and numerous honorary degrees and awards, including the Lasker Special Achievement Award in Medical Science in 1999. He died in 2000.

Holzman PS. Seymour S. Kety 1915–2000. Nature Medicine 2000;6(7):727.
Sokoloff L. In Memoriam. Seymour S. Kety 1915–2000. Am J Med Genet (Neuropsychiatric Gen) 2000;96:585–589.

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 he opposed the approach of Sigmund Freud, who viewed and treated mental disorders as secondary to psychological factors.

Kraepelin proposed that psychiatric diseases should 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 before 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 20th century, Kraepelin's contributions were marginalized because of the success of Freudian theories of mental illness. However, his fundamental concepts on the etiology and diagnosis of psychiatric disorders form the bases of all major diagnostic systems used today, most notably the American Psychiatrics Association's DSM-IV and the World Health Organization's *International Classification of Diseases* (ICD) system.

Kraepelin was born in 1856 in Germany. Having chosen a career in psychiatry at the young age of 18 years, 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 years 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.

Images in Psychiatry. Am J Psychiatry 2006;163:1710.
Images in Psychiatry. Am J Psychiatry 1994;151:3.
Braceland FJ. Kraepelin, His System and His Influence. Am J Psychiatry 1957;113:871–876.

Charles Philippe Leblond

Charles Philippe Leblond was a Canadian anatomist 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. C. P. 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.

C. P. Leblond was born in Lille, France in 1910 and received his medical degree from the University of Paris in 1934. After 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. C. P. Leblond returned to the Department of Anatomy at McGill as an associate professor, becoming department

FIGURE 40.20.

FIGURE 40.21.

chair in 1957, a position in which he served until 1974. C. P. 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, Leblond was appointed Officer of the Order of Canada. He died in 2007.

http://www.thecanadianencyclopedia.com/index.cfm?PgNm=TCE&Params=A1ARTA0004600

Charles Philippe Leblond. Protoplasm 1991;160(1):3.

Bennet G, Bergeron J. Charles Leblond 1910–2007. Nat Cell Biol 2007;9:707–723.

Rita Levi-Montalcini

Rita Levi-Montalcini is 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 and 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 has been the recipient of many awards and honors for her work on NGF, including induction into the United States National Academy of Sciences in 1968 and the Nobel Prize for Physiology or Medicine (along with Stanley Cohen) in 1986.

http://nobelprize.org/nobel_prizes/medicine/laureates/1986/press.html

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, Lorenz 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.

Lorenz 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

FIGURE 40.22.

FIGURE 40.23.

the following paradox: all of 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.

Lorenz KZ. The evolution of human behavior. Sci Am 1958 Dec;199(6):67–74.

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. Before 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 patients 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 before 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.

Fink M, Ladislas J. Meduna, MD. 1896–1964. Am J Psychiatry 1999;156:1807.
Fink M. Historical Article: Autobiography of L.J. Meduna. Convuls Ther 1985;1:43–57;121–135.
Meduna LJ. Oneirophrenia: The Confusional State. Urbana: University of Illinois Press, 1950.

Herbert Y. Meltzer

Herbert Meltzer is an American psychiatrist 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 United States. Meltzer's research demonstrated that clozapine was effective in reducing the risk of suicide in schizophrenic patients 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

FIGURE 40.24.

FIGURE 40.25.

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 MD from Yale University in 1963 and received his psychiatric training at the Massachusetts Mental Health Center. Meltzer has been professor of psychiatry at the University of Chicago and Case Western Reserve University and is currently Bixler Professor of Psychiatry and Pharmacology and Director of the Division of Psychopharmacology at the Vanderbilt University School of Medicine. 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 Psychiatrists.

http://www.precisionmed.com/about2.html
https://medschool.mc.vanderbilt.edu/facultydata/php_files/part_dept/show_part.php?id3=1033
http://www.medscape.com/viewarticle/519981
Healy D. Herbert Meltzer: A career in biological psychiatry. In: The Psychopharmacologists: Interviews. London: Altman, an imprint of Chapman and Hall, 1996:483–507.

António Caetano de Abreu Freire Egas Moniz

Antonio 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 allowed physicians to map blood vessels in and around the brain, permitting the diagnosis of several kinds of neurological disorders, including 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 also in emotions). 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.

Moniz E. I succeeded in performing the prefrontal leukotomy. J Clin Exp Psychopathol 1954;15(4):373–379.
http://nobelprize.org/nobel_prizes/medicine/laureates/1949/moniz-bio.html

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

FIGURE 40.26.

FIGURE 40.27.

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 that 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.

Franz Nissl (1860–1919), neuropathologist. JAMA 1968;205(6): 460–461.

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 who 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 to the United States, 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 by Japan where his image appears on a stamp and, since 2004, on the 1,000 Yen note.

Haas LF. Neurological stamp: Hideo Noguchi (1897–1928). J. Neurol Neurosurg Psychiatry 2002;73(2):147.
http://www.rockefeller.edu/benchmarks/benchmarks_060704_d.php

John William Olney

John William Olney is an American psychiatrist 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, because too much glutamate stimulation was shown to destroy nerve cells, a condition he referred to as "excitotoxicity." Through subsequent research, Olney has identified excitotoxicity as a mechanism that causes neurodegeneration seen with acute brain injury, including stroke and trauma. Research that is more recent has 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 has received many awards and honors throughout his career, including the Wakeman award, the Society for Biological Psychiatry Lifetime Achievement Award, and membership in the Institute of Medicine of the National Academy of Sciences.

http://www.dbbs.wustl.edu/dbbs/website.nsf/FLUP2/6EAFF068E483EF8286256D4E005B2D81?OpenDocument
http://www.psychiatry.wustl.edu/c/Faculty/FacultyDetails.aspx?ID=282
Olney JW, Faber NB. Glutamate receptor dysfunction and schizophrenia. Arch Gen Psychiatry 1995;52(12):998–1007.

FIGURE 40.28.

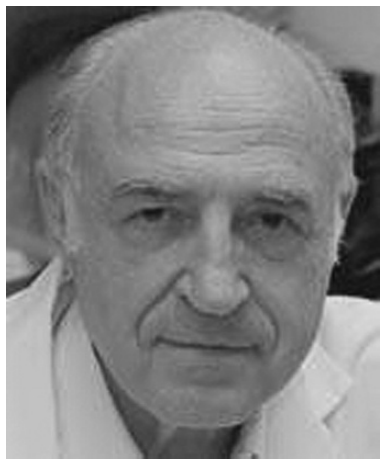

FIGURE 40.29.

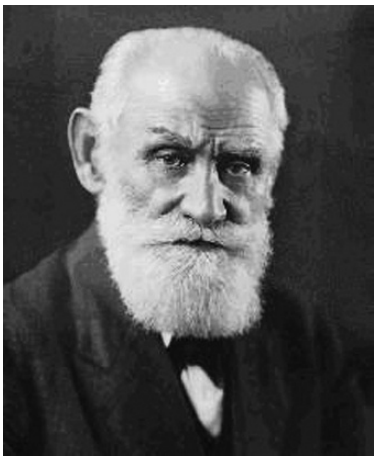

FIGURE 40.30.

FIGURE 40.31.

Ivan Petrovich Pavlov

Ivan 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.

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, such as salivation, that only occurred conditionally on specific previous experiences of the animal. He died in 1936.

http://nobelprize.org/nobel_prizes/medicine/laureates/1904/pavlov-bio.html

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 infirmaries" at Bicêtre Hospital. At the time, it housed approximately 4,000 imprisoned men—criminals, petty offenders, syphilitics, pensioners, and approximately 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 the patients 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. Pinel died in 1826.

Pinel P. A Treatise on Insanity, in which are contained the principles of a new and more practical nosology that has been offered to the public. Translated by Davis DD. London: Cadwell and Davies, 1806.

Pasko Rakic

Pasko Rakic is a Yugoslavian-born American 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

FIGURE 40.32.

FIGURE 40.33.

also provided insight into developmental plasticity by discovering that neurons overproduce projections, synapses, and signaling molecules, which are later selectively pruned back because of 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.

Dr. Pasko Rakic receives the 15th Annual Bristol-Myers Squibb Neuroscience Award for discovering the basis of neuronal migration in brain development. Neuroscientist 2003;9:221–230.
Dove A. Pasko Rakic. Nat Med 2005;11(4):362.

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 he 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-IV. Together with George Murphy, Robins launched the first detailed 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 more than 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.

Sullivan R. Dr. Eli Robins, 73, challenger of Freudian psychiatry, is dead. New York Times, February 11, 1995:50.
Rich CL. In memoriam and memorial service. Eli Robbins, M.D. Ann Clin Psychiatry 1995;7(1):1–10.
http://outlook.wustl.edu/winter2006/suicide.html

Kurt Schneider

German psychiatrist Kurt Schneider worked to improve psychiatric diagnosis and, in the tradition of Kraepelin and Jaspers, thought 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 "first 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 rebuild German medical facilities, Schneider was appointed as Dean of the Medical School at Heidelberg University,

FIGURE 40.34.

FIGURE 40.35.

where he remained until his retirement in 1955. He died in 1967.

Carpenter WT, Strauss JS. Cross-cultural Evaluation of Schneider's First Rank Symptoms of Schizophrenia. Am J Psychiatry 1974;131:6.

Philip Seeman

Philip Seeman was born in Winnipeg, Canada in 1934. He received an MD from McGill University (1960). He had a rotating internship at Detroit's Harper Hospital, and subsequently received his PhD 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 cross-appointed as a Professor of 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 anaesthetic-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 receptor by using 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 during the lifespan. 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 stayed 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 to 900%. These elevated $D2^{High}$ states seem 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, seem 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.

http://www.utoronto.ca/seeman/

Seeman P, Chau-Wong M, Tedesco J, Wong K. Brain receptors for antipsychotic drugs and dopamine: direct binding assays. Proc Natl Acad Sci USA 1975;72(11):4376–4380.

Seeman P. Dopamine D2 (High) receptors on intact cells. Synapse. 2008;62(4):314–318.

B. F. Skinner

Burrhus Frederick Skinner was an American psychologist and author best known for his pioneering work in experimental

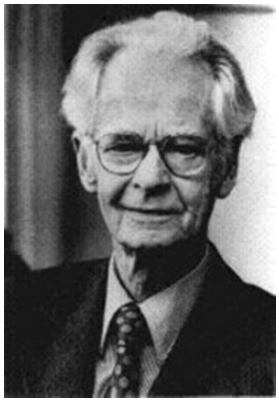

FIGURE 40.36.

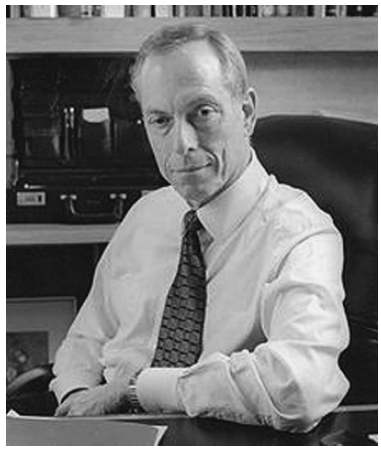

FIGURE 40.37.

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 after any behavior, leading the behavior, 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 that 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, he was awarded the Gold Medal of the American Psychological Association. He died of leukemia in 1990.

Epstein R. Skinner as self-manager. Journal applied behavior analysis. 1997;30:545–569.
http://www.bfskinner.org/bio.asp

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, and bradykinin receptor, as well as several receptors for serotonin and he co-discovered 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 discoveries and 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 years. 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 that 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.

http://www.iom.edu/?id=15526
http://www.jhu.edu/news_info/news/home05/feb05/medal.html
http://www.jhu.edu/~jhumag/0400web/03.html

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 epileptic patients 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,

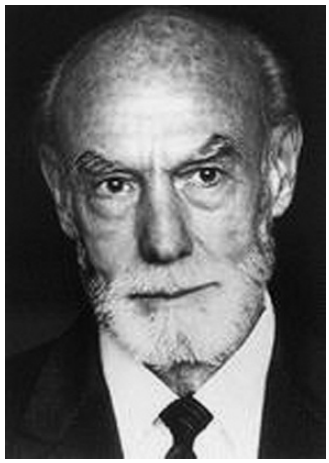

FIGURE 40.38.

FIGURE 40.39.

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.

Nobelprize.org biography

Baruch Spinoza

Baruch Spinoza was a Dutch mathematician and 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 should be detached from external cause 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 regarding 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.

Popkin RH Spinoza. Oxford: One World Publications, 2004.
Spinoza B. Ethics. Edited and translated by Parkinson GHR. New York: Oxford University Press, 2000.

Earl W. Sutherland, Jr.

Earl Sutherland was an American biochemist who first discovered and characterized cyclic adenosine monophosphate (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 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 another second messenger on the inside of the cell, activating or inhibiting various cellular processes.

FIGURE 40.40.

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 director of the department of medicine 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.

http://nobelprize.org/nobel_prizes/medicine/laureates/1971/press.html

Porter R, Ogilvie M. The Biographical Dictionary of Scientists, volume 2, 3rd ed. New York: Oxford University Press, 2000.

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 the proponent of the infectious etiology for schizophrenia. Before 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 schizophrenic patients. 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.

FIGURE 40.41.

Torrey is also the founder and currently the executive director of the Stanley Medical Research Institute, which is the largest private provider of grant support for research on schizophrenia and bipolar disorder in the United States and has resulted in the publication of over 240 papers on the molecular basis of schizophrenia, bipolar disorder and depression.

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.

Torrey E, Yolken RH. Toxoplasma gondii and schizophrenia. Emerg Infect Dis 2003;9(11):1375–1380.

Fatemi SH, ed. Neuropsychiatric Disorders and Infection. London: Taylor & Francis; 2005.

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.

http://nobelprize.org/nobel_prizes/medicine/laureates/1927/wagner-jauregg-bio.html

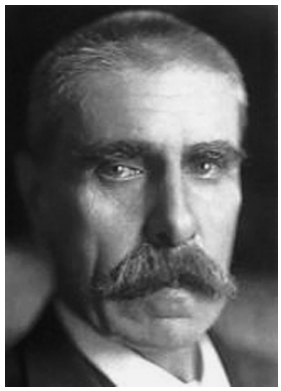

FIGURE 40.42.

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 or Feighner criteria, which proposed diagnostic criteria for 14 psychiatric illnesses, in association with Samuel Guze and Eli Robbins, among others. The criteria were not intended as final but rather as a framwork that could be amended as new information became available. Accordingly, the criteria provided a model for psychiatric diagnostic criteria that would later become enshrined in DSM-III, DSM-III-R, and DSM-IV. 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. After his retirement in 1995, Winokur continued his research activities until his death in 1996.

Feighner JP, Robins E, Guze SB, Woodruff RA Jr, Winokur G, Munoz R. Diagnostic criteria for use in psychiatric research. Arch Gen Psychiatry 1972;26:57–63.

Tsuang MT. Images in psychiatry. Am J Psychiatry 1999;156(3): 465–466.

FIGURE 40.43.

41
Normal Laboratory Values and Drug Therapeutic and Toxic Ranges

S. Hossein Fatemi, MD, PhD

TABLE 41.1. Selected normal Laboratory values used in psychiatry.

Test	Conventional units	SI units
Alanine aminotransferase (ALT)[a]	≤35 U/L	≤0.58 μkat/L
Albumin[a]	3.5–5.5 g/dL	35–55 g/L
Alkaline phosphatase[a]	30–120 U/L	0.5–2.0 nkat/L
Aluminum[a]	<5.41 μg/L	<0.2 μmol/L
Ammonia (NH_3)[b]	10–80 μg/dL	6–47 μmol/L
Amylase[a]	60–180 U/L	0.8–3.2 μkat/L
Androstenedione[a]	50–250 ng/dL Postmenopausal: <180 ng/dL	1.75–8.73 nmol/L Postmenopausal: <6.3 nmol/L
Anion gap	7–16 mmol/L	7–16 mmol/L
Antidiuretic hormone (ADH) (arginine vasopressin hormone)[b]	≤2.2 pg/mL with serum osmolality <285 mOsm/kg; 2.2–8.5 pg/mL with serum osmolality >290 mOsm/kg	≤2.2 ng/L with serum osmolality <285 mOsm/kg; 2.2–8.5 ng/L with serum osmolality >290 mOsm/kg
Anti-DNA antibody (double stranded)[a]	Negative at 1:10 dilution	
Antimicrosomal antibody (thyroid) [a]	<0.3 IU/mL	<300 U/L
Antimitochondrial antibody[a]	Negative	
Antinuclear antibody (ANA)[a]	Negative at 1:40 dilution	
Antithyroglobulin antibody[a]	Negative	
Arsenic[c]	<50 μg/24 h	<0.65 μmol/24 h
Arterial blood gasses		
$[HCO_3^-]$	21–30 mEq/L	21–28 mmol/L
P_{CO_2}	35–45 mmHg	4.7–5.9 kPa
pH	7.38–7.44	7.38–7.44
P_{O_2}	80–100 mmHg	11–13 kPa
Aspartate aminotransferase (AST)[a]	≤35 U/L	<0.58 μkat/L
Bilirubin[a]		
Direct	<0.3 mg/dL	<5.1 μmol/L
Indirect	<0.7 mg/dL	<12 μmol/L
Bilirubin total[a]	<1.0 mg/dL	<17 μmol/L

From: S. H. Fatemi and P. J. Clayton (eds.): *The Medical Basis of Psychiatry*

TABLE 41.1. (continued)

Test	Conventional units	SI units
Cadmium[d]	≤2 μ g/L (nonsmoker)	≤17.8 nmol/L (nonsmoker)
Calcitonin[a]	Male: 3–26 pg/mL Female: 2–17 pg/mL	Male: 3–26 ng/L Female: 2–17 ng/L
Calcium Serum Urine (on 200 mg/day dietary calcium) Calcium, ionized[a]	 9–10.5 mg/dL Male: <300 mg/day Female: <250 mg/day 4.5–5.6 mg/dL	 2.2–2.6 mmol/L Male: <7.5 mmol/day Female: <6.2 mmol/day 1.1–1.4 mmol/L
Carbohydrate-deficient transferrin[a]	Male: <20 units/L Female: <26 units/L	Male: <27 units/L Female: <35 units/L
Carbon dioxide[a]	21–30 mEq/L	21–30 mmol/L
Carotene[a]	50–300 μg/dL	0.9–5.6 μmol/L
Catecholamines fractionated[b]	Dopamine Supine: <87 pg/mL Standing: <87 pg/mL Epinephrine Supine (30 minutes): <50 pg/mL Sitting: <60 pg/mL Standing (30 minutes): <900 pg/mL Norepinephrine Supine (30 minutes): 110–410 pg/mL Sitting: 120–680 pg/mL Standing (30 minutes): 125–700 pg/mL	Dopamine Supine: <475 pmol/L Standing: <475 pmol/L Epinephrine Supine (30 minutes): <273 pmol/L Sitting: <328 pmol/L Standing (30 minutes): <4, 914 pmol/L Norepinephrine Supine (30 minutes): 650–2423 pmol/L Sitting: 709–4019 pmol/L Standing (30 minutes): 739–4137 pmol/L
Ceruloplasmin[a]	27–37 ng/dL	270–370 mg/L
Cerebrospinal fluid (CSF) Glucose Lactate Total protein Lumbar Cisternal Ventricular Albumin IgG IgG index Oligoclonal bands (OGB) Ammonia CSF pressure CSF volume (adult) Red blood cells Leukocytes Total Differential Lymphocytes Monocytes Neutrophils	 40–70 mg/dL 10–20 mg/dL 15–50 mg/dL 15–25 mg/dL 6–15 mg/dL 6.6–44.2 mg/dL 0.9–5.7 mg/dL – – 25–80 μg/dL 50–180 mmH_2O – 0	 2.22–3.89 mmol/L 1–2 mmol/L 0.15–0.5 g/L 0.15–0.25 g/L 0.06–0.15 g/L 0.066–0.442 g/L 0.009–0.057 g/L 0.29–0.59 <2 bands not present in matched serum sample 15–47 μmol/L – ∼150 mL 0 0–5 mononuclear cells per mm^3 60–70% 30–50% None
Chloride[a]	98–106 mEq/L	98–106 mmol/L
Cholesterol, total[a]	Desireable: <200 mg/dL Borderline–high: 200–239 mg/dL High: ≥240 mg/dL	Desireable: <5.17 mmol/L Borderline–high: 5.17–6.18 mmol/L High: ≥6.21 mmol/L
Complement[a] (adults) C3 C4 Total (CH50)	 86–184 mg/dL 20–58 mg/dL 63–145 U/mL	 0.86–1.84 g/L 0.20–0.58 g/L 63–145 kU/L
Complete blood count (CBC) Hemoglobin (Hb)[d] Hematocrit (Hct)[d] RBC count[d]	 Male: 13.5–17.5 g/dL Female: 12.0–16.0 g/dL Male 41–53% Female: 36–46% Male 4.5–5.9 × $10^6/mm^3$ Female: 4.0–5.2 × $10^6/mm^3$	 Male: 8.4–10.9 mmol/L Female: 7.4–9.9 mmol/L Male 0.41–0.53 Female: 0.36–0.46 Male 4.5–5.9 × 10^{12}/L Female: 4.0–5.2 × 10^{12}/L

TABLE 41.1. (continued)

Test	Conventional units	SI units
RBC indices[d]	Mean corpuscular volume	Mean corpuscular volume
	Males: 78–100 μm^3	Males: 78–100 fL
	Females: 78–102 μm^3	Females: 78–102 fL
	Mean corpuscular Hb: 26–34 pg/cell	Mean corpuscular Hb: 26–34 pg/cell
	Mean corpuscular Hb concentration: 31–37 g/dL	Mean corpuscular Hb concentration: 310–370 g/L
	RBC distribution width: 11.5–14.5%	RBC distribution width: 0.115–0.145
WBC count[d]	4.5–11.0 $\times 10^3/mm^3$	4.5–11.0 $\times 10^9/L$
WBC differential[d]	Absolute neutrophils: 1,500–7,800 cells/μL	Absolute neutrophils: 1.5–7.8 $\times 10^9/L$
	Absolute eosinophils: 50–550 cells/μL	Absolute eosinophils: 0.05–0.55 $\times 10^9/L$
	Absolute basophils: 0–200 cells/μL	Absolute basophils: 0–0.2 $\times 10^9/L$
	Absolute lymphocytes 850–4,100 cells/μL	Absolute lymphocytes 0.85–4.10 $\times 10^9/L$
	Absolute monocytes 200–1100 cells/μL	Absolute monocytes 0.2–1.1 $\times 10^9/L$
Platelet count[d]	150–350 $\times 10^3/mm^3$	150–350 $\times 10^9/L$
Copper[a]	70–140 μg/dL	11–22 μmol/L
Cortisol, free[c]	20–70 μg/24 h	55–193 nmol/24 h
Cortisol[a]	5–25 μg/dL (fasting, 8 am to noon)	138–690 nmol/L (fasting, 8 am to noon)
	0–10 μg/dL (8 pm to 8 am)	0–276 nmol/L (8 pm to 8 am)
C-Peptide[a] (insulin)	0.78–1.89 ng/mL	0.26–0.62 nmol/L
C-Reactive protein (CRP)[a]	<8 mg/L	<8 mg/L
Creatine kinase (CK)		
Isoenzymes[a]	CK-MM: 97–100% of total	CK-MM: 0.97–1.00 of total
	CK-MB: <3% of total	CK-MB: <0.03 of total
	CK-BB: 0% of total	CK-BB: 0 of total
Total:	Male: 60–400 U/L	Male: 1.00–6.67 μkat/L
	Female: 40–150 U/L	Female: 0.67–2.50 μkat/L
Creatinine		
Serum	$\leq$1.5 mg/dL	$\leq$133 μmol/L
Urine (creatine)	Male: <50 mg/24 h	Male: <380 μmol/24h
	Female: <100 mg/24 h	Female: <760 μmol/24h
Clearance (inulin) mean $\pm$1 SD	Male: 124 $\pm$ 25.0 mL/min	Male: 2.1 $\pm$ 0.4 mL/sec
	Female: 119 $\pm$ 12.8 mL/min	Female: 2.0 $\pm$ 0.2 mL/sec
Cyanide[d]	<0.1 mg/L	<3.8 μmol/L
Erythrocyte sedimentation rate (ESR)[d]	Male: $\leq$17 mm/h	Male: $\leq$17 mm/h
	Female: $\leq$25 mm/h	Female: $\leq$25 mm/h
Erythropoietin[a]	5–36 U/L	5–36 U/L
Estradiol[a]	Male: <20 pg/mL	Male: <184 pmol/L
	Female	Female
	Follicular phase: <20–145 pg/mL	Follicular phase: 184–532 pmol/L
	Mid-cycle peak phase: 112–443 pg/mL	Mid-cycle peak phase: 411–1626 pmol /L
	Luteal phase: <20–241 pg/mL	Luteal phase: 184–885 pmol /L
	Postmenopausal: <59 pg/mL	Postmenopausal: <217 pmol /L
Ferritin[a]	Male: 15–400 ng/mL	Male: 15–400 μg/L
	Female: 10–200 ng/mL	Female: 10–200 μg/L
Folic acid		
RBC	150–450 ng/mL cells	340–1020 nmol/L cells
Serum	3–16 ng/mL cells	7–36 nmol/L cells
Follicle-stimulating hormone (FSH)[a]	Male: 1–12 U/L	Male: 1–12 U/L
	Female	Female
	Follicular phase: 3–20 U/L	Follicular phase: 3–20 IU/L
	Ovulatory phase: 9–26 U/L	Ovulatory phase: 9–26 IU/L
	Luteal phase: 1–12 U/L	Luteal phase: 1–12 IU/L
	Pregnancy: <0.9 U/L	Pregnancy: <0.9 IU/L
	Postmenopausal: 18–153 U/L	Postmenopausal: 18–153 IU/L
Gastrin[a]	<200 pg/mL (nonfasting)	<200 ng/L (nonfasting)
	<100 pg/mL (fasting)	<100 ng/L (fasting)
Glucagon[b]	20–100 pg/mL	20–100 ng/L
Glucose		
Fasting[b]	75–115 mg/dL	4.2–6.4 mmol/L
Diabetes mellitus[a]	>125 mg/dL	>7.0 mmol/L

TABLE 41.1. (continued)

Test	Conventional units		SI units	
Glucose-6-phosphate dehydrogenase (G6PD)[d]	5–3 U/g Hb		5–3 U/g Hb	
Glucose tolerance test (GTT)				
General[b]	2-hour postload (75-g oral glucose load): <140 mg/dL		2-hour postload: <7.8 mmol/L	
Obstetric[b]	Screening test (50-g oral glucose load)	Diagnostic test (100-g oral glucose load)	Screening test (50-g oral glucose load)	Diagnostic test (100-g oral glucose load)
	Fasting: –	<105 mg/dL	Fasting: –	<5.8 mmol/L
	1 hour: <140 mg/dL	<190 mg/dL	1-hour: <7.8 mmol/L	<10.5 mmol/L
	2 hours –	<165 mg/dL	2 hours: –	<9.2 mmol/L
	3 hours: –	<145 mg/dL	3 hours: –	<8.0 mmol/L
γ- Glutamyltransferase (GGT)[a]	1–94 U/L		1–94 U/L	
Growth hormone (GH)[a] (resting)	0.5–17 ng/mL		0.5–17 μg/L	
Hematocrit (Hct) [d]	Male: 41–53% Female: 36–46%		Male: 0.41–0.53 Female: 0.36–0.46	
Hemoglobin (Hb)[d]	Male: 13.5–17.5 g/dL Female: 12.0–16.0 g/dL		Male: 8.4–10.9 mmol/L Female: 7.4–9.9 mmol/L	
A_{1c}	<6.0% of total Hb		<0.06 of total Hb	
High-density lipoprotein (HDL)[a]	<40 mg/dL "Negative" risk factor: ≥60 mg/dL		≥0.164 mmol/L "Negative" risk factor: ≥1.55 mmol/L	
Homocysteine[b]	4–12 μmol/L		4–12 μmol/L	
Homovanillic acid[c]	≤10 mg/day		≤55 μmol/day	
Human chorionic gonadotropin (hCG)				
Qualitative[c]	Nonpregnant: negative Pregnant: positive		Nonpregnant: negative Pregnant: positive	
Quantitative (intact and free β)[a]	Male: <2 IU/L Female Premenopausal: <5 IU/L Postmenopausal: <10 IU/L Pregnancy 0–2 weeks <500 IU/L 2–3 weeks 100–5,000 IU/L 3–4 weeks 500–10,000 IU/L 1–2 months 1,000–200,000 IU/L 2–3 months 10,000–100,000 IU/L		Male: <2 IU/L Female Premenopausal: <5 IU/L Postmenopausal: <10 IU/L Pregnancy 0–2 weeks <500 IU/L 2–3 weeks 100–5,000 IU/L 3–4 weeks 500–10,000 IU/L 1–2 months 1,000–200,000 IU/L 2–3 months 10,000–100,000 IU/L	
17-Hydroxycorticosteroids[c]	Male: 3–15 mg/24 h Female: 2–12 mg/24 h		Male: 8.3–41.4 μmol/24 h Female: 5.5–33.1 μmol/24 h	
5-Hydroxyindoleacetic acid (5-HIAA)[c]	2–7 mg/24 h		10.5–36.6 μmol/24 h	
Immunoglobulin[a]				
IgA	60–309 mg/dL		0.6–3.09 g/L	
IgD	≤14 mg/dL		≤0.14 g/L	
IgE	<180 IU/mL		<432 μg/L	
IgG subclasses	Subclass IgG1: 270–1740 mg/dL Subclass IgG2: 30–630 mg/dL Subclass IgG3: 13–320 mg/dL Subclass IgG4: 11–620 mg/dL		Subclass IgG1: 2.7–17.4 g/L Subclass IgG2: 0.3–6.3 g/L Subclass IgG3: 0.13–3.2 g/L Subclass IgG4: 0.11–6.20 g/L	
IgG, total	614–1295 mg/dL		6.14–12.95 g/L	
IgM	53–334 mg/dL		0.53–3.34 g/L	
Insulin[a,b]	2–20 μU/mL		14.35–143.5 pmol/L	
Iron[a]	50–150 μg/dL		9–27 μmol/L	
Iron-binding capacity[a]	250–370 μg/dL % Saturation: 20-45%		45-66 μmol/L % Saturation: 0.2–0.45	
Lactate dehydrogenase (LD)[a]				
Isoenzymes	LD1: 14–26% of total LD2: 29–39% of total LD3: 20–26% of total		LD1: 0.14–0.26 of total LD2: 0.29–0.390 of total LD3: 0.20–0.26 of total	

TABLE 41.1. (continued)

Test	Conventional units	SI units
	LD4: 8–16% of total LD5: 6–16% of total	LD4: 0.08–0.16 of total LD5: 0.06–0.16 of total
Total	100–190 U/L	1.7–3.2 μkat/L
Lactic acid (venous)[b]	5–15 mg/dL	0.6–1.7 mmol/L
Lead[b] (adult)	<10–20 μg/dL	<0.5–1.0 μmol/L
Lipase[a]	23–300 U/L	0–2.66 μkat/L
Low-density lipoprotein (LDL) cholesterol, direct[a]	Desirable: <100 mg/dL Borderline–high: 130–159 mg/dL High: ≥160 mg/dL	Desirable: <2.58 mmol/L Borderline–high: 3.36–4.11 mmol/L High: ≥4.14 mmol/L
Luteinizing hormone (LH)[a]	Male: 2–12 U/L Female Follicular phase: 2–15 U/L Ovulatory phase: 22–105 U/L Luteal phase: 0.6–19.0 U/L Pregnancy: <1.4 U/L Postmenopausal: 16–64 U/L	Male: 2–12 U/L Female Follicular phase: 2–15 U/L Ovulatory phase: 22–105 U/L Luteal phase: 0.6–19.0 U/L Pregnancy: <1.4 U/L Postmenopausal: 16–64 U/L
Lymphocyte surface markers (T cell)[d]		
CD3	Absolute: 840–3060 cells/μL Percentage: 57–85%	Absolute: 0.84–3.06 × 10^9 cells/L Percentage: 57–85%
CD4	Absolute: 490–1740 cells/μL Percentage: 30–61%	Absolute: 0.49–1.74 × 10^9 cells/L Percentage: 30–61%
CD8	Absolute: 180–1170 cells/μL Percentage: 12–42%	Absolute: 0.18–1.17 × 10^9 cells/L Percentage: 12–42%
Helper/suppressor (CD4/CD8) ratio	0.86–5.00	0.86–5.00
Magnesium[a]	1.8–3.0 mg/dL	0.8–1.2 mmol/L
Mercury		
Urine	<20 μg/L	<99.8 nmol/L
Blood	0.6–59 μg/L	3.0–294 nmol/L
Metanephrines[c]		
Fractionated	Metanephrine: <0.4 mg/24 h Normetanephrine: <0.9 mg /24 h	Metanephrine: <2.2 μmol /24 h Normetanephrine: <4.9 μmol /24 h
Total	<1.3 mg/24 h	<7.1 μmol/24 h
Methemoglobin[d]	<1% of total Hb	<0.01 of total Hb
Microalbumin		
24-hour urine	<20 mg/L or <31 mg/24 h	<0.2 g/L or < 0.031g/24 h
Spot am urine	<0.03 mg albumin/mg creatinine	<0.03 g albumin/g creatinine
Myelin basic protein[e]	<4 ng/mL	<4 μg/L
Myoglobin[a]		Male: 19–92 μg/L Female: 12–76 μg/L
Nitrogen, total[f]	<1.7 g/24 h	<1.7 g/24 h
Osmolality	3.1–14 ng/mL[a] 300–900 mOsm/kg[c]	3.1–14 ng/mL[a] 300–900 mmol/kg[c]
Oxalate[c]	20–60 mg/24 h	228–684 μmol/24 h
Parathyroid hormone (PTH)[a] intact	10–60 pg/mL	10–60 ng/L
Partial thromoplastin time (PTT) activated[b]	22.1–35.1 sec	22.1–35.1 sec
Phosphorus, inorganic[a]	3.0–4.5 mg/dL	1.0–1.45 mmol/L
Platelet count[d]	150–350 × 10^3/mm^3	150–350 × 10^9/L
Porphobilinogen[c]	≤ 2 mg/24 h	≤ 8.8 μmol/24 h
Potassium[a]	3.5–5.0 mEq/L	3.5–5.0 mmol/L
Prealbumin[a]	19.5–35.8 mg/dL	195–358 mg/L
Progesterone[a]	Male: <1.2 ng/mL Female Follicular phase: <1.0 ng/mL Luteal phase: 3–20 ng/mL Pregnancy First trimester 9.0–47.0 ng/mL Second trimester 17.0–146.0 ng/mL	Male: <3.8 nmol/L Female Follicular phase: <3.18 nmol/L Luteal phase: 9.54–63.6 nmol/L Pregnancy First trimester 28.6–149.5 nmol/L Second trimester 54.1–464.3 nmol/L

TABLE 41.1. (continued)

Test	Conventional units	SI units
	Third trimester 55.0–255.0 ng/mL Postmenopausal: <0.7 ng/mL	Third trimester 174.9–810.9 nmol/L Postmenopausal: <2.2 nmol/L
Prolactin[a]	Male: 1.6–23.0 ng/mL Female Nonpregnant: 1.9–25.9 ng/mL Pregnant: 10–209 ng/mL Postmenopausal: 2–20 ng/mL	Male: 0–15 μg/L Female Nonpregnant: 0–20 μg/L Pregnant: 10–209 μg/L Postmenopausal: 2–20 μg/L
Prostate specific antigen (PSA)[a] (male)	<40 years: 0–2 ng/mL >40 years: 0–4 ng/mL	<40 years: 0–2 μ g/L >40 years: 0–4 μ g/L
Protein, total	5.5–8.0 g/dL[a] <150 mg/day[c]	55–80 g/L[a] <150 mg/day[c]
Protein electrophoresis[a]	Albumin: 3.5–5.5 g/dL α_1 - Globulins: 0.2–0.4 g/dL α_2 - Globulins: 0.5–0.9 g/dL β - Globulins: 0.6–1.1 g/dL γ - Globulins: 0.7–1.7 g/dL Total globulins: 2–3.5 g/dL	Albumin: 35–55 g/L α_1 - Globulins: 2–4 g/L α_2 - Globulins: 5–9 g/L β - Globulins: 6–11 g/L γ - Globulins: 7–17 g/L Total globulins: 20–35 g/L
Prothrombin time (PT)[b]	11.1–13.1 sec	11.1–13.1 sec
Protoporphyrin[d] Free erythrocyte Zinc	 <36 μg/dL RBCs <70 μg/dL	 <0.64 μmol/L RBCs <700 μg/L
Pyruvate[d] (venous)	0.5–1.5 mg/dL	60–170 μmol/L
Renin activity[b] (normal sodium diet)	1–9 ng/mL/h (upright) 0.3–3.0 ng/mL/h (supine)	0.28–2.5 ng/L-s (upright) 0.08–0.83 ng/L-s (supine)
Reticulocyte count[d]	0.5–2.5% of RBCs	0.005–0.025 of RBCs
Rheumatoid factor[a]	<30 IU/mL	<30 kIU/L
Serotonin[d] Platelets	50–200 ng/mL 125–500 ng/10^9 platelets	0.28–1.14 μmol/L 0.7–2.8 amol/platelet
Sodium[a]	136–145 mmol/L	136–145 mmol/L
Somatomedin-C (IGF-1) (adult)[a]	16–24 years: 182–780 ng/mL 25–39 years: 114–492 ng/mL 40–54 years: 90–360 ng/mL >54 years: 71–290 ng/mL	16–24 years: 182–780 μg/L 25–39 years: 114–492 μg/L 40–54 years: 90–360 μg/L >54 years: 71–290 μg/L
Somatostatin[b]	<25 pg/mL	<25 ng/L
T_3 (triiodothyronine)[a] Free Reverse Total	 1.4–4.4 pg/mL 2.6–18.9 ng/dL 60–181 ng/dL	 0.22–6.78 pmol/L 0.04–0.29 nmol/L 0.9–2.8 nmol/L
T_4 (thyroxine)[a] Free Total	 0.8–2.7 ng/dL 4.5–10.9 μg/dL	 10–35 pmol/L 58–140 nmol/L
Testosterone, total[a] (morning sample)	Male: 270–1070 ng/dL Female: 6–86 ng/dL	Male: 9.36–37.10 nmol/L Female: 0.21–2.98 nmol/L
Thrombin time[b]	16–24 sec	16–24 sec
Thyroglobulin[a]	≤60 ng/mL	≤60 μg/L
Thyroid hormone binding index[a] (THBI or T_3RU)	0.83–1.17	0.83–1.17 mol ratio
Thyroid-stimulating hormone (TSH), ultrasensitive (third generation)[a]	0.50–4.70 μU/mL	0.50–4.70 mU/L
Thyroxine-binding globulin (TBG)[a]	16–24 μg/dL	206–309 μg/L
(Free) Thyroxine index[a]	4.2–13	4.2–13
Transferrin[a]	230–390 mg/dL	2.3–3.9 g/L
Triglycerides[a]	<160 mg/dL	<1.8 mmol/L
Troponin I[a]	0–0.4 ng/mL	0–0.4 μg/L
Troponin T[a]	0–0.1 ng/mL	0–0.1 μg/L
Urea nitrogen, blood (BUN)[a]	10–20 mg/dL	3.6–7.1 mmol /L
Uric acid Serum Urine	 Male: 2.5–8.0 mg/dL Female: 1.5–6.0 mg/dL 200–750 mg/24 h	 Male: 150–480 μmol/L Female: 90–360 μmol/L 1.2–4.5 mmol/24 h

TABLE 41.1. (continued)

Test	Conventional units	SI units
Urinalysis, complete[c]	Appearance: clear, yellow Specific gravity: 1.001–1.035 pH: 5.0–9.0 Protein: negative Glucose: negative Reducing substances: negative Ketones: negative Bilirubin: negative Occult blood: negative WBC esterase: negative Nitrite: negative WBC: ≤2/high-power field RBC: ≤2/high-power field Renal epithelial cells: ≤3/high-power field Squamous epithelial cells: none or few/high-power field Casts: none Bacteria: none Yeast: none	
Vanillylmandelic acid (VMA)[c]	0.15–1.2 mg/24 h	7.6–37.9 μmol/24 h
Vasoactive intestinal polypeptide (VIP)[b]	<75 pg/mL	<75 ng/L
Vitamin A[a]	20–100 μg/dL	0.7–3.5 μmol/L
Vitamin B_1 (thiamine)[a]	0–2 μg/dL	0–75 nmol/L
Vitamin B_2 (riboflavin)[a]	4–24 μg/dL	106–638 nmol/L
Vitamin B_6[b]	5–30 ng/mL	20–121 nmol/L
Vitamin B_{12}[a]	200–800 pg/mL	148–590 pmol/L
Vitamin C[b]	0.4–1.0 mg/dL	23–57 μ mol/L
1,25–Dihydroxyvitamin D_3[a]	24–45 pg/mL	60–108 pmol/L
25-Hydroxyvitamin D_3[b]	Summer: 15–80 ng/mL Winter: 14–42 ng/mL	Summer: 37.4–200 nmol/L Winter: 34.9–105 nmol/L
Vitamin E[a]	5–18 μg/mL	12–42 μmol/L
Vitamin K[a]	0.13–1.19 ng/mL	0.29–2.64 nmol/L
Coenzyme Q_{10} (ubiquinone)[b]	0.5–1.5 μg/mL	0.5–1.5 mg/L
Zinc[b]	75–120 μg/dL	11.5–18.5 μmol/L

[a] Serum.
[b] Plasma.
[c] Urine.
[d] Blood.
[e] CSF.
[f] Feces.

μkat, microkatal; L, liter (1,000 ml); U, unit; g, gram; dL, deciliter (100 ml); nmol, 10^{-9} mole; pg, picogram or 10^{-12} of a gram; mOsm, milliosmolal; KU, kilounit; amol, attomol or 10^{-18} mol.

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TABLE 41.2. Therapeutic range and toxicity of selected drugs.

	Therapeutic range		Toxic range	
Drug	Conventional units	SI units	Conventional units	SI units
Acetaminophen[a]	10–30 μg/mL	66–199 μmol/L	>200 μg/mL	>1, 324 μmol/L
Amantadine[a]	200–1,000 ng/mL		>2, 000 ng/mL	
Amitriptyline and its metabolite, nortriptyline, total[a]	120–250 ng/mL	433–903 nmol/L	>500 ng/mL	>1, 805 nmol/L
Amobarbital[a]	3–12 mg/L	13–53 μmol/L		
Amphetamine[a]	20–30 ng/mL	148–222 nmol/L	>200 ng/mL	>1, 480 nmol/L
Barbiturates, most short-acting[a]			>20 mg/L	>88 μmol/L
Bupropion hydroxybupropion[a]	50–100 ng/mL 600–2000 ng/mL		>170–300 ng/mL n.d.	n.d. n.d.
Buspirone[a]	Peak: 100–800 ng/mL Trough: 40–350 ng/mL		n.d.	n.d.
Carbamazepine[a]	6–12 μg/mL	26–51 μmol/L	>15 μg/mL	>63 μmol/L
Chlordiazepoxide and metabolite, desmethylchlordiazepoxide total[a]	700–1000 ng/mL	2.34–3.34 μmol/L	>5, 000 ng/mL	>16.7 μmol/L
Chlorpromazine[a]	30–300 ng/L	157–942 nmol/L	>750 ng/mL	>2, 355 nmol/L
Citalopram[a]	Up to 120 ng/mL		n.d.	
Clomipramine and its metabolite desmethylclomipramine, total[a]	70–200 ng/mL 150–300 ng/mL 220–500 ng/mL		>1, 000 ng/mL	
Clonazepam[a]	15–60 ng/mL	48–190 nmol/L	>80 ng/mL	>254 nmol/L
Clorazepate[a]	0.4–1.5 mg/L	1.20–4.52 μmol/L	>5, 000 ng/mL	>150 μmol/L
Clozapine and its metabolite norclozapine[a]	200–350 ng/mL >450 ng/mL	0.6–1 μmol/L	>1, 800 ng/mL	5.4 μmol/L
Cocaine			>1, 000 ng/mL	>3, 300 nmol/L
Cyclosporine[b] (depends on timing after dose and transplant type)	Kidney transplant: 100–400 ng/mL	83–333 nmol/L		
Desipramine[a]	75–300 ng/mL	281–1125 nmol/L	>400 ng/mL	>1, 500 nmol/L
Diazepam and its metabolite N-desmethyl-diazepam, total[a]	0.3–1.5 μg/mL	1.05–5.3 μmol/L	>5, 000 ng/mL	>17.55 μmol/L
Digoxin[a]	0.8–2.0 ng/mL	1.0–2.6 nmol/L	>2.5 ng/mL	>3.2 μmol/L
Doxepin and its metabolite desmethyldoxepin, total[a]	150–250 ng/mL	540–900 nmol/L	>500 ng/mL	>1, 790 mmol/L
Ethanol Behavioral changes Intoxication	 >20 mg/dL >100 mg/dL	 >4.3 mmol/L >1 g/L		
Fluoxetine and its metabolite norfluoxetine, total[a]	300–1,200 ng/mL	867–3,468 nmol/L	>2, 000 ng/mL	>5, 784 nmol/L
Fluphenazine[a]	0.3–3.0 ng/mL	0.6–6.0 ng/mL	>50 ng/mL	>98 nmol/L
Fluvoxamine[a]	50–900 ng/mL		n.d.	
Haloperidol[a]	5–20 ng/mL	10–40 nmol/L	>42 ng/mL	84 nmol/L
Ibuprofen[a]	10–50 μg/mL	49–243 μmol/L	100–700 ng/mL	485–3395 μmol/L
Imipramine and its metabolite desipramine, total[a]	100–300 ng/mL	350–1,070 nmol/L	>500 ng/mL	>1, 784 nmol/L
Lamotrigine (free)	1–9 μg/mL		n.d.	n.d.
Lithium[a] • Acute mania • Polyuria, blurred vision, lethargy, weakness, increased reflexes, fasiculations • Myoclonus, incontinence, stupor, restlessness, coma • Seizures, hypotension, arrhythmias • Coma, death	0.6–1.2 mEq/L 0.8–1.0 mEq/L	0.6–1.2 mmol/L 0.8–1.0 mmol/L	 1.5–2.25 mEq/L 2.5–3.0 mEq/L >3.0 mEq/L >4.0 mEq/L	 1.5–2.25 mmol/L 2.5–3.0 mmol/L >3.0 mmol/L >4.0 mmol/L
Lorazepam[a]	50–240 ng/mL	156–746 nmol/L	>500 ng/mL	>1, 560 nmol/L
Loxapine	30–100 ng/mL			
Meprobamate[a]	6–12 μg/mL	27–55 μmol/L	>60 μg/mL	>275 μmol/L
Methadone[a]	100–400 ng/mL	0.32–1.29 μmol/L	>2, 000 ng/mL	>6.4 μmol/L
Methotrexate[a] Low dose (1–2 weeks) High dose (48 hours)	Variable	Variable	 >9.2 ng/mL >227 ng/mL	 >20 nmol/L >0.5 μmol/L

TABLE 41.2. (continued)

Drug	Therapeutic range		Toxic range	
	Conventional units	SI units	Conventional units	SI units
Molindone[a]	30–70 ng/mL		>200 ng/mL	
Morphine[a]	10–80 ng/mL	35–280 μmol/L	>200 ng/mL	>700 nmol/L
Nortriptyline[a]	50–150 ng/mL	190–570 nmol/L	>500 ng/mL	>1.9 μmol/L
Olanzapine	10–80 ng/mL		n.d.	
Oxazepam[a]	200–500 ng/mL	0.7–4.9 μmol/L	>2, 000 ng/mL	>70 μmol/L
Paroxetine[a]	20–200 ng/mL		n.d.	
Pentobarbital[a]	1–5 μg/mL	4–22 μmol/L	>50 μg/mL	>220 μmol/L
Perphenazine	0.8–2.4 ng/mL			
Phenobarbital[a]	10–40 μg/mL	43–170 μmol/L		
Slowness, ataxia, nystagmus			35–80 μg/mL	151–345 μmol/L
Coma with reflexes			65–117 μg/mL	280–504 μmol/L
Coma without reflexes			>100 μg/mL	>430 μmol/L
Phenytoin[a]	10–20 μg/mL	40–79 μmol/L	>20 μg/mL	>79 μmol/L
Propranolol[a]	50–100 ng/mL	193–386 nmol/L	>1, 000 ng/mL	>3860 nmol/L
Salicylate[a]	150–300 μg/mL	1,086–2,172 μmol/L	300 μg/mL	>2,172 μmol/L
Sertraline and desmethylsertraline[a]	30–200 ng/mL		>500 ng/mL	
Theophylline[a]	8–20 μg/mL	44–111 μmol/L	>20 μg/mL	>110 μmol/L
Thioridazine	1–1.5 ng/mL			
Thiothixene	2–15 ng/mL			
Trazodone[a]	800–1,600 ng/mL		>5, 000 ng/mL	
Trifluoperazine[a]	4–40 ng/mL		>50 ng/mL	
Valproic acid[a]	50–150 μg/mL	347–1, 040 μmol/L	>150 μg/mL	>1, 040 μmol/L
Venlafaxine and desmethylvenlafaxine[a]	200–400 ng/mL			
Verapamil[a]	50–250 ng/mL	100–510 nmol/L	>250 ng/mL	>510 nmol/L
Zolpidem[a]	Up to 250 ng/mL		n.d.	

[a] Serum.
[b] Blood.

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